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COMMITTEE PRINT

INTERNATIONAL MEDICAL RESEARCH

A COMPILATION OF BACKGROUND MATERIALS

PREPARED FOR THE

COMMITTEE ON GOVERNMENT OPERATIONS

UNITED STATES SENATE

AND ITS

SUBCOMMITTEE ON REORGANIZATION AND INTERNATIONAL ORGANIZATIONS

PURSUANT TO S. RES. 347, 85TH CONGRESS

November 10, 1958

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LETTER OF TRANSMITTAL

UNITED STATES SENATE,
November 10, 1958.

Hon. JOHN L. MCCLELLAN,
Chairman, Senate Committee on Government Operations,
United States Senate, Washington, D. C.

MY DEAR MR. CHAIRMAN: The subcommittee submits for your consideration the attached summary of certain selected material on the subject of International Medical Research.

The summary is intended for background purposes in the initial phases of review by our colleagues and by interested officials and members of the public.

In the period ahead there will be submitted additional factual materials prepared at the request of the subcommittee by agencies of the Federal Government, by other expert sources, and by the subcommittee staff as further background to work under Senate Resolution 347, 85th Congress.

The subcommittee plans an intensive series of reviews within the United States and abroad, prior to the preparation of its detailed findings.

With kindest wishes, I am,
Sincerely yours,

HUBERT H. HUMPHREY,
Chairman, Subcommittee on Reorganization and International Organizations.

FOREWORD

By Hon. Hubert H. Humphrey, Chairman, Subcommittee on Reorganization and International Organizations

Senate Resolution 347 of the 85th Congress, approved August 18, 1958, authorized the Senate Committee on Government Operations "to make a complete study of any and all matters pertaining to international health, research, rehabilitation, and assistance programs."

The resolution was based on recognition of two facts:

1. Mankind's efforts for the conquest of disease have become a matter of ever higher priority in the judgment of the American people and of the Congress. Consequently—

2. A comprehensive study of these efforts may help clarify problems and opportunities in present and future endeavors against the scourge of killing and crippling disease.

The present committee print represents the first of a series of publications designed for purposes of background to this study.

Subsequent publications will elaborate on the broad variety of activities in which the Government and people of the United States are engaged in international medical research and health activities.

A few initial facts may serve to indicate the dimensions of overall medical research.

The final report [1] of the Consultants on Medical Research and Education to the Secretary of Health, Education, and Welfare contains pertinent helpful data.

First, it reports:

> **The world is experiencing a scientific and technological revolution that will leave no aspect of human life untouched. Medical research, like other areas of science, will become broader in dimension and more penetrating in depth. * * * The fruits of medical research will be further prolongation of life and relief of suffering. A byproduct of medical research will be a marked increase in physical and mental capabilities of the population.**

MEDICAL RESEARCH IN RELATION TO OVERALL RESEARCH

The report enumerates these statistics, among others:

In 1957 total national medical research aggregated $330 million. By contrast, 10 years earlier it had totaled $88 million.

In 1957 the Federal Government contributed 56 percent of total medical research funds; private industry, 27 percent; philanthropy, 11 percent; and endowment, 6 percent. (A decade earlier

[1] The Advancement of Medical Research and Education Through the Department of Health, Education, and Welfare, Office of the Secretary, Department of Health, Education, and Welfare, June 27, 1958.

the respective proportions had been: Federal, 32 percent; industry, 40 percent; philanthropy, 17 percent; endowment, 11 percent.)

In 1957, with a gross national product of $434 billion, $10 billion was devoted to national research and development in all fields. This represented 2.3 percent of gross national product. In turn, medical research, as such, represented 3.3 percent of the total outlay for overall research and development.

By 1970 the consultants "believe it conservative to project national medical research expenditures of $900 million to $1 billion per year."

This is based on certain assumptions, among which are the following: (*a*) That the United States will enjoy a gross national product of $640 billion in 1970; (*b*) that the proportion of gross national product represented by all types of research and development will rise gradually from the current level of 2.3 percent to 4 percent by 1970; and (*c*) that the proportion of overall research and development expenditures represented by medical research, as such, will remain constant at the average of the past decade—3.8 percent.

It should be noted now that—

(*a*) Only a very small, but a rising, proportion of present medical research funds are for *international* activities, as such.

(Of course, *domestic* research, conducted in the continental United States, contributes to and draws from the pool of medical research throughout the world.)

(*b*) The figures do *not* include international medical *service* activities, the application of knowledge, as distinguished from research.

(By such *service* activities is basically meant the broad variety of public-health efforts to help uplift standards in the underdeveloped areas of the world.

(To raise such standards necessarily involves significant prior research efforts, because all medical and public health advances essentially stem from research.)

It should be noted that this committee print is devoted to research, as such; future publications will concentrate on medical service.

MANY AGENCIES ENGAGED IN RESEARCH, SERVICE

Numerous Federal agencies are engaged in medical-biological research and in international health-assistance efforts. On the research side, the agencies with principal duties include the Department of Health, Education, and Welfare, the Veterans' Administration, the National Science Foundation, the Atomic Energy Commission, and the Department of Defense.

American health service activities abroad in underdeveloped areas of the world are a responsibility of the International Cooperation Administration, working in conjunction with the Department of State. In addition, the United States contributes significantly to world health through its activities in the United Nations and its specialized agencies, notably, the World Health Organization.

INTEREST OF COMMITTEE ON GOVERNMENT OPERATIONS

Here, then, is a subject of such deep interest to the Government of the United States, involving so many interrelated Federal activities

at home and abroad, that it well bears the attention of the committees of the United States Congress.

The Committee on Government Operations has a broad-gaged interest, arising out of its responsibilities under the legislative reorganization law.

As indicated in Senate Report 360, 85th Congress, by which the Senate Committee on Rules favorably reported Senate Resolution 347, rule XXV of the Standing Rules of the Senate provides that the Committee on Government Operations has the duty of—

> studying the operations of Government activities at all levels, with a view to determining its economy and efficiency [and the further duty] of studying international relationships between the United States * * * and international organizations of which the United States is a member.

By the decision of the chairman of this committee, the Honorable John McClellan, of Arkansas, the study contemplated under Senate Resolution 347 has been entrusted to the Subcommittee on Reorganization and International Organizations. This subcommittee has been engaged during the 85th Congress in a review of somewhat related subject matter involving science, in general, in the United States.

In its initial activity, pursuant to Senate Resolution 347, the subcommittee has already contacted a broad variety of expert sources, at home and abroad. Within the Congress itself the subcommittee recognizes and respects the jurisdictions of other standing committees of the Senate in the health and related fields. The subcommittee has invited and received assurances of the cooperation of such other committees.

LIMITED PURPOSES OF THIS PRINT

In proceeding to its task, the subcommittee felt at the outset the need to have readily available in summary form, certain selected background material on the subject of international medical research.

The purpose of this committee print is, therefore, to help fulfill this need. Attention, however, is directed to the fact that this initial compendium is not all inclusive. Indeed, it is in no way intended as either a comprehensive or definitive review of the subject. Each of the principal sections of the print is intended solely as a preliminary outline of the subjects depicted. Neither the time available for the preparation of this material, nor brevity of space, permit anything more than a brief exposition.

FOURFOLD CONTENTS OF PRINT

The contents of this print include—

Some of the highlights of international research contributions in most of the major fields of disease.

A description of the means of scientific communication throughout the world.

A brief review of the history of medical research in the United States.

Material on the activities of the Public Health Service in international medical research.

It should be stated that the section on Public Health Service activities presents a picture of how PHS, as the principal Federal agency

concerned with health, is currently meeting its research responsibilities in collaboration with other nations. These responsibilities stem from the obligations of the Service under law to conduct and support activities for the ultimate improvement of the health of the people of the United States.

The materials on the Public Health Service, which deal largely with its main research arm, the National Institutes of Health, are concerned with research, research training, and the communication of research information.

APPRECIATION

Appreciation is hereby expressed to Dr. Leroy Burney, Surgeon General of the United States Public Health Service, whose ready cooperation has enabled the subcommittee to proceed rapidly in its work. In addition, the subcommittee gratefully acknowledges the specific assistance of Dr. James Shannon, Director of the National Institutes of Health. Acting upon the request of this committee, Dr. Shannon and his staff compiled the material herein with customary diligence and dispatch.

It is fitting that the National Institutes should have been called upon as the expert source of factual information in this print. The high regard which the Congress of the United States feels for this great organization is a matter of public record, and needs no elaboration here. Suffice it to add, however, that NIH fulfills not only the fundamental creed of medicine, but symbolizes in many significant respects, the devotion to man's well-being on the part of this Republic, itself.

The healing arts, throughout man's history, have always provided inspiration, but perhaps never more so than in the present age of scientific discovery. It is, of course, paradoxical that, at this very time, when man has within his capacity heretofore unforeseen powers of potential mass destruction, man likewise has developed unprecedented powers for improving the health of the human family.

TEAMWORK BY ALL EXPERT SOURCES

It is the hope of men of good will everywhere that more and more the energies of all nations may be channeled to the constructive purpose of furthering the well-being of man.

In this effort, increased teamwork is essential. This includes—

The teamwork of all of the life sciences; for they find that increasingly the work under their respective disciplines comes to overlap as related resources are mobilized in probing further and further into the unknown;

Teamwork of the great system of private medicine, and of all of the members of professions allied to medicine—of the private pharmaceutical and chemical industries whose research contributions grow with each passing day;

Between the broad variety of American foundations, voluntary health agencies, universities, institutes, hospitals, and other organizations interested in health at home and abroad; and

Within and between the governments of the nations of the world themselves.

RESEARCH IS INTERNATIONAL

Medical research itself has always had an international character. Medicine has been the beneficiary of discoveries which have transcended national boundaries. Today the complexity and volume of medical research render especially important the promptest possible exchange of scientific information and strengthened cooperation. In this way, precious time and effort may be saved and used to best advantage.

Modern methods of communication and transportation render such cooperation ever more feasible. As the world has shrunk through jet aviation and other transportation, cooperative efforts have become especially obligatory against the spread of infectious diseases, for they can now span continents with speed heretofore impossible.

This committee print, limited as its contents necessarily are, may provide at the outset a measure of perspective as to the past, the present, and the future. It may help, therefore, to aid not only in the study by our subcommittee, but in some small way as a stimulus to efforts by men of good will everywhere in the furtherance of man's health and welfare.

There is no politics or ideology in a cancer cell. A child in any nation, suffering from, for example, leukemia, evokes anguish in the heart of parents and other loved ones, and sympathy everywhere. Men are linked by common pain and suffering. Men are linked also by the common joy of conquering disease and disability.

Modern science is unlocking riddles which have baffled man from the dawn of time. The secrets of life are being unfolded, including mysteries of the cell. No man now can fully foresee how future discovery may benefit men everywhere. Within the pages which follow is an outline of what men have achieved and are achieving now in medical research; the future lies in our hands.

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PART 1

SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN MAJOR AREAS OF MEDICAL RESEARCH

THE SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN GENERAL MEDICAL SCIENCE

CLASSIC CONTRIBUTIONS

The Father of Medicine.—Hippocrates (460–377 B. C.), Greek physician, is called the father of medicine. This man, who is considered by many to be the greatest of the great classical physicians, wrote voluminously on epidemics, fevers, epilepsy, fractures, health in general, and medical ethics. Today, as they have done throughout the centuries, physicians in nearly all countries subscribe to the Oath of Hippocrates.

The First Widespread Text in Medicine.—Avicenna (980–1037) of Persia, the most illustrious physician in Arabian medicine, codified the whole of medical knowledge up to his time. This work, the *Canon*, was translated into Latin and became the authoritative medical textbook in Europe for six centuries. It is still considered infallible in Islam.

Early Observations on Anemias.—Johannes Lange (1485–1565), one of the most highly esteemed physicians of the 16th Century, received his M. D. degree in Pisa in 1522. He continued to study and practice in various countries of Europe, and in 1554 published a treatise on nutritional anemias, one of the first such writings known. Interestingly, he prescribed marriage as a means of curing young girls afflicted with such anemias, this circumstance apparently awakening the victim's interest in food.

First Great Anatomist.—Andreas Vesalius (1514–1564) of Brussels, issued his masterpiece of anatomy, *De Humanis Corporis Fabrica*, at Basel in 1543, containing illustrations which were executed in the workshop of the master painter Titian. This volume, together with its companion, *Epitome*, remains paramount among the centuries' products in descriptive anatomy.

First Man to See Bacteria.—Anton van Leeuwenhoek (1632–1723), pioneer Dutch microscopist, was the first actually to see single-cell organisms such as bacteria, and gave the first accurate description of the red blood cell.

Early Description of Liver Disease.—John Brown (1642–1700), who came of a long line of English surgeons, was trained at St. Thomas's Hospital, London. He served as surgeon to Charles II and later to William III. Brown described quite accurately the disease entity known as cirrhosis (hardening) of the liver. The actual name cirrhosis was applied 100 years later by Laënnec.

First Clear Description of Pellagra.—Gaspar Caśal (1679–1759), known as the "Spanish Hippocrates," practiced medicine in Madrid. In 1751 he was appointed physician to King Ferdinand. Caśal wrote the first clear description of pellagra (niacin deficiency) in 1735,

applying the name "mal de la Rosa" to the condition. The name derives from the reddish hue which is assumed by areas of the skin of pellagrous individuals.

First Good Study of Digestion.—Lazaro Spallanzani (1729–1799), Italian physiologist, demonstrated for the first time that the secretions of the stomach have the ability to dissolve meat, using a buzzard as his experimental subject. For research equipment, Spallanzani used a piece of meat on a string. Studies of the processes of digestion soon became widespread, due to Spallanzani's pioneer discoveries.

First Experimental Pathologist.—John Hunter (1728–1793), Scottish surgeon in England, contributed much toward the development of experimental pathology, and wrote a classic description of inflammation in 1794. His experimental subjects were persons suffering with gunshot wounds.

Together with his brother, William, John Hunter established a school of anatomy; and one of his students, Edward Jenner (1749–1823), later discovered the means of vaccinating against smallpox.

A medical museum containing many well-preserved examples of diseased organs prepared by Dr. Hunter is still maintained in London, and may be visited today.

NINETEENTH AND TWENTIETH CENTURY LANDMARKS

The First Stethoscope.—René Laënnec (1781–1826) received his M. D. at the Charité Hospital, Paris, in 1804. He invented the stethoscope in 1816, an achievement which assured the immortality of his name. Laënnec's original stethoscope was a roll of paper, which later developed into a hollow wooden cylinder. Laënnec, who devoted much of his professional life to the study of patients with chest disease, died of tuberculosis.

The Childbed Fever Problem.—Ignaz Semmelweis (1818–1865), obstetrician in Vienna, was the first to recognize that the prevailing 50 percent death rate of women hospitalized for childbirth was due to bacterial contamination by the unwashed hands of attending physicians. His fellow physicians, slow to recognize his discovery, so derided and persecuted Semmelweis that he committed suicide. In later years hygienic practices based upon the writings of Semmelweis decreased the deaths from childbed fever to less than 1 percent.

First Geneticist.—Greger Johann Mendel (1822–1884), an Austrian monk and scientist, discovered the fundamental principles governing inheritance of characteristics passed on by parents to offspring. Comprehension of such diseases as hemophilia rests to a large degree on an understanding of Mendelian genetics.

X-Rays.—Wilhelm K. Roentgen (1845–1923), German scientist, discovered X-rays in 1895, and laid the foundation for the science of radiology. He was awarded a Nobel prize for this work in 1901.

Science of Body Salts.—Svante A. Arrhenius (1859–1927), of Sweden, developed the theory which describes the existence of electrically charged particles in solution. For this he was awarded a Nobel prize in 1903, and from his theory developed the basis for modern fluid- and salt-balance therapy used in practically all hospitals throughout the world.

Vitamins.—Frederick G. Hopkins (1861–1947), of England, predicted the discovery of vitamins in 1906, and as a result of isolating some growth-promoting substances at this early date was awarded a Nobel prize in 1929.

Founders of the Science of Radiation.—Marie Curie (1867–1934), working in France with her husband Pierre and Henri Becquerel, discovered radium in 1898. These three scientists received a Nobel award for work on radioactivity in 1903, and later Marie Curie received another Nobel award in 1911. Radium therapy has found an established place in modern medicine, and the new field of radioisotopes is just now coming into its own.

Safe Blood Transfusions.—Karl Landsteiner (1868–1943), American, established in 1900 the basis for classifying blood into groups, and with Alexander Wiener discovered the Rh factor in 1940. For the original work on blood groups, Dr. Landsteiner received the Nobel prize in 1930. The methods he devised for typing blood are in universal use today, and are saving untold millions of lives.

Insulin and Sugar Diabetes.—Frederick Banting (1891–1941), Canadian, together with John McLeod (1876–1935), discovered insulin in 1922. As a result, millions of diabetics are afforded a reasonably normal life. These two men were awarded a Nobel prize in 1923.

PRESENT FOREIGN RESEARCH OF GREAT PROMISE IN THE FIELD OF GENERAL MEDICINE

Belgium.—Dr. Corneille Heymans (Nobel laureate, 1938), University of Ghent, 3, Albert Baertsoenkaai, Ghent; fundamental research on respiration.

England.—Dr. Watson Crick, Cambridge University; studies on the basic structure of cell proteins.

Dr. Hans Krebs (Nobel laureate, 1953), Department of Biochemistry, Oxford; fundamental metabolism research.

Dr. A. T. Welford, Psychological Laboratory, Cambridge University; psychological studies on aging industrial workers.

France.—Dr. F. Bourlière, Claude Bernard Center of Gerontology, Paris; comparative zoologic studies in aging.

Dr. Latarget, Director of Pasteur Institute, Paris; studies on effects of radiation on living matter.

Germany.—Dr. Adolf Butenandt (Nobel laureate, 1939), Max Planck Institute for Biochemistry, Munich; isolated, identified, and synthesized the sex hormones; has pioneered the field of chemical genetics.

Dr. Gerhard Domagk (Noble laureate, 1939), I. G. Farben Laboratory, Elberfeld; studies on biochemistry of metabolism.

Dr. Gunther Lehmann, Max Planck Institute for Physiology of Work, Dortmund; studies on effects of aging and other factors on work capacity in the Ruhr mining district.

Dr. Max Schneider, Institute of Physiology, University of Cologne, Cologne; studies on cell and tissue metabolism.

Gerhard Schramm, Max Planck Institute for Virus Research, Tuebingen; fundamental studies on metabolism.

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Otto Warburg (Nobel laureate, 1931), Max Planck Institute for Cell Physiology, Berlin Dahlem; studies on the chemistry of cell respiration.

Holland.—Dr. J. Groen, Wilhelmina Gasthuis, Amsterdam; aging and nutrition studies.

Sweden.—Hans von Euler (Nobel laureate, 1929), Vitamin Institute, Stockholm; fundamental biochemical studies.

Switzerland.—Dr. F. Verzar, University of Basel, Basel; environmental stresses and aging.

NOTE.—The task of individually assigning proper credit for great medical-scientific discoveries is a difficult and often impossible undertaking. In acknowledging the outstanding work of the individuals afore-mentioned, the committee would feel remiss if it failed to mention mankind's indebtedness to innumerable other individuals, perhaps less well known, who contributed to the continuous unfoldment and refining of discovery which characterizes scientific research.

SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN CARDIOVASCULAR MEDICINE

The earliest medical writings show some knowledge of the blood and the importance of the heart as one of the primary organs of the body. An ancient Egyptian papyrus of around 1500 B. C. and Chinese writings of 500 B. C. recorded pulse lore. Aristotle, Hippocrates, and Leonardo da Vinci were among those who studied movements of the heart and the blood system. That heart disease could be chronic was first demonstrated clearly in 1507. But the Greek physician Galen's theory—that the blood ebbed and flowed like the tide—had a strong hold until the 17th century.

BEGINNINGS OF HEART RESEARCH

Heart research really began in 1628 when William Harvey, an English physician working in London, published his findings that the heart pumped the blood continuously in the body. This research made it possible for Harvey's successors to study the heart for what it is—a muscle and a pump. Working painstakingly for over 20 years on animals, Dr. Harvey laid the groundwork for modern physiology and experimental medicine of the 19th century.

The University of Padua in Italy, where Harvey received his first medical degree, also fostered Fabricius, Harvey's teacher, and Andreas Vesalius, a Belgian, who became the founder of modern anatomy in 1543.

Early Clinical Advances.—Clinical discoveries came along slowly, with many set-backs. Bonet of France recognized in 1679 the relationship of shortness of breath to enlargement of the heart, and sudden death associated with calcification of the aorta. At the beginning of the 18th century, the coronary circulation and mitral stenosis and its symptoms were explained by Vieusseus, of France. Lancisi of Italy, physician to Pope Clement XI, described in 1707 cardiac and aortic enlargement and produced the first treatise on sudden death with autopsy findings. Jean Baptiste De Senac, a Frenchman, gave advice about treatment as well as diagnosis, and published in 1749 the first preponderantly clinical work on heart disease. Heberden, in 1768 lectured in England on a disorder of the breast which he called angina pectoris. A few years later Louis Jenner, a London physician, established the connection between angina pectoris and coronary artery disease.

Early Diagnostic Advances.—Tools for studying the heart and circulation were developed gradually.

By inserting a glass tube into the leg of a mare, Stephen Hales, an English clergyman with a scientific mind, first devised a method for measuring the pressure of the blood (1733).

Leopold Auenbrugger, an Austrian doctor and musician, discovered in 1761 that he could diagnose the size of an enlarged heart and determine accumulation of fluid by applying the art of tapping or percussion.

Early Therapeutic Advances.—The first great forward step in treatment came in 1785, when Dr. William Withering, an English physician and botanist, gave to the world a great drug of enduring value even today—digitalis.

The preceding classics of cardiovascular history are some of those which form the basis of modern medicine.

MAJOR LANDMARKS IN THE NINETEENTH AND TWENTIETH CENTURIES: A SELECTION

Beginning of Modern Clinical Medicine.—The nineteenth century produced many notable contributions to our knowledge of the heart and circulation—but perhaps the greatest single discovery was the introduction of the stethoscope and auscultation by René-Theophile-Hyacinth Laënnec (France, 1819). This, along with Jean-Nicolas Corvisart's (France, 1806) revival and augmentation of Leopold Auenbrugger's (Austria, 1761) method of percussion, completed the quartet of modern physical diagnosis: inspection (estimating size by the visible apex impulse), palpation (feeling with the hand), percussion (thumping with the hand or hammer), and auscultation (listening with the stethoscope). As a direct result of this broadening of the methods of diagnosis, great impetus was given to the more precise recognition and classification of diseases of the heart.

The Heart and Kidney Disease.—One of the most brilliant contributions of the 19th century is credited to Richard Bright (England, 1827), who gave his name to a kidney disease which is now more accurately known to the medical profession as nephritis. Bright described a part of the kidney's function in circulation and showed how impaired heart action leads to dropsy.

Introduction of the X-ray.—Virtually all branches of medicine have profited by the genius of Nobel prize winner Wilhelm Konrad Röentgen (Germany, 1895), but few have benefited as rapidly and to the degree that cardiology has. Within one year the use of X-rays was applied to problems of the heart. One of the first, if not the first, to develop its use in cardiology was Francis Henry Williams (U. S. A., 1896).

Early Twentieth Century Landmark.—The electrocardiograph came less than eight years after the introduction of X-rays when Nobel prize winner Willem Einthoven (Holland, 1903) described his findings with a string galvanometer he adapted to record the electrical impulses in the heart. This basic principle is behind today's electrocardiograph machines, required equipment for most practitioners.

The Pacemaker.—In the average healthy heart, regular impulses are sent out from a tiny structure—a highly specialized mass of tissue in the right auricle—at a rate of about seventy per minute. Two men, Sir Arthur Keith and Martin Flack (England, 1907) discovered its existence. They presumed this "sinus node" to be the pacemaker of the human heart, but did not prove it. Several years later Sir Thomas Lewis (England, 1909), one of the world's greatest cardiologists, proved that this node was the site of impulse origin.

Coronary Thrombosis.—The first truly representative and influential account regarding the clinical recognition of coronary thrombosis was that of James Bryan Herrick (U. S. A., 1912).

Congestive Heart Failure.—The use of mercurial diuretic injections in the treatment of cardiac edema (lymph swelling) had its origin in the work of P. Saxl (Austria, 1920). Since then, with the advent of more refined and safer mercurial diuretics, it has revolutionized the treatment of congestive heart failure and proved to be one of the greatest therapeutic innovations of all time.

Congenital Heart Surgery.—The first congenital heart defect to yield to surgery was the patent ductus arteriosus (an embryonic vessel that sometimes fails to close at birth). This operation was performed by Dr. Robert E. Gross (U. S. A., 1939).

Anti-Coagulant.—Dr. Karl Paul Link (U. S. A., 1940) and his associates are given credit for discovering the anti-coagulant, dicumarol. First used to avert clots after operations, it began to be used in 1942 for patients who had coronary thrombosis.

Pioneering Surgery.—Normal color and vitality are denied "blue babies" because of a combination of congential heart defects that robs the blood of oxygen and the tissues of nourishment. Now, because of an ingenious operation devised by Drs. Alfred Blalock and Helen B. Taussig (U. S. A., 1945), surgeons can relieve the situation.

That same year, Dr. Clarence Crafoord (Sweden, 1945) corrected another congenital heart defect with the first operation on a human for coarctation of the aorta, an abnormal narrowing of the body's main blood trunkline.

Surgery Within the Heart.—The preceding operations were all performed upon tissues outside the heart—the aorta, or vessels leading off from the aorta or the pulmonary artery. No one had operated successfully upon tissues within the heart. Then, four years later, Dr. Charles Bailey (U. S. A., 1949) announced the accomplishment of this feat. He cut through the heart wall and inserted a tiny finger-knife between the lips of the narrowed mitral valve. In this way he was able to restore normal size and function to a valve scarred by rheumatic fever.

The Last Ten Years.—In the last ten years, important heart research advances have come in such profusion and variety—open heart surgery, hypotensive drugs, blood vessel grafts, rheumatic fever prevention, and new knowledge of the mechanisms of atherosclerosis, to name a few—and so many important international research figures are associated with each, one is tempted to say that the era of individual and widely separated "landmarks" has given way to a time when peaks abound.

Today, there are many peaks, surrounded by many peaks—the interdependent work of innumerable men and minds. But only the luxury of the future can help us to see these contributions in their proper perspective.

HIGHLIGHTS OF PRESENT RESEARCH ABROAD

Today thousands of scientists are working all over the world to add new knowledge to the understanding of heart disease. In the present as in the past a partial truth laboriously developed in one part of the world may spark the imagination of a scientist on the other side of

the earth, or may lie dormant for years. A scientist trained in one country may become a Nobel prizewinner for work done in another part of the world. Medical research is a worldwide affair.

A résumé is presented of some of the cardiovascular research now going on in other countries.

England.—Sir James Mackenzie and Sir Thomas Lewis are two outstanding clinicians who have contributed to experimental cardiology. Working at the Institute of Cardiology in London, Dr. Maurice Campbell is carrying on research in congenital heart defects and, at present, is concentrating on the diagnosis and correction of ventricular septal defects. Sir Russell Brock, also working in London, is recognized for his work on congenital defects of the heart. Dr. Paul Wood, at the London Institute of Cardiology, is studying pulmonary circulation, and Dr. Samuel Oram at Kings College Hospital, has made contributions to the field of electrocardiography in pulmonary embolism. Professor T. McKeown, M. D., of Birmingham, is studying the causes of congenital malformations. Michael F. Oliver in Edinburgh is doing research in arteriosclerosis. George White Pickering in London is noted for his studies on circulatory physiology and causes of arteriosclerosis. Dr. E. G. L. Bywaters in Maidenhead carries out clinical studies of rheumatic fever. Dr. Patrick Mounsey is a member of the staff of the Cardiology Department of London Hospital. He is working on phonocardiography and has made investigations of patent ductus. Dr. J. N. Morris of London is making comparative studies of populations and groups in relation to heart diseases. In Sheffield, Professor C. H. Stuart-Harris, M. D., is studying pulmonary heart disease.

France.—France has long enjoyed a tradition of excellent original scientific thought, and the work produced in cardiology is no exception. Working today in Paris is Dr. Jean Lenegre. He is interested in clinical electrocardiology and has made special contributions in pulmonary hypertension of mitral stenosis and catheterization of the right heart.

Highly regarded heart surgeons today in Paris include J. Mathey, specializing in acquired heart diseases, P. Soulie, working chiefly with congenital heart disease, and Francois Allaines.

C. Lian has made contributions to phonocardiography, and Edouard Donzelot is a Paris Professor doing research on heart and blood vessels.

One of the most distinguished of modern cardiologists is Professor A. F. Cournand, a recent Nobel prize winner who was trained and began his work in France. In the U. S. A. since 1931, Dr. Cournand is widely recognized for his work on catheterization of the heart.

Italy.—A good deal of cardiovascular research is going on in several of the chief university towns of Italy. In Rome, Dr. Luigi Condorelli is making contributions in radiological methods, congenital anomalies, and pulmonary hypertension. Also at Rome is Vittorio Puddu who has done work in the epidemiology of atherosclerosis and in rheumatic fever.

National Heart Institute grantees C. A. Montagnani and V. Venturi, at the University of Florence, are seeking knowledge about the anatomy of the circulation in prenatal and newborn infants.

Among the noted heart surgeons are Pietro Valdoni, who has done special work on pulmonary embolism, and A. M. Dogliotti in Turin. In Genoa is E. Malan whose work on peripheral vascular diseases is widely recognized. Galeno Ceccarelli, director of surgery in the University of Padua, is both a practicing surgeon and a researcher.

Germany.—At the present time, Dr. H. Schaefer and Dr. Trautwein at the Physiology Institute in Heidelberg are making notable progress in electrokymography. Dr. H. Reichel, Dr. R. Wagner, and Dr. E. Wetterer at the Physiology Institute in Munich are investigating blood pressure regulation and curves of cardiac equilibrium in cold-blooded animals.

Dr. K. Rothschuh and Dr. E. Schutz at the Physiology Institute in Munster are working on heart sounds and electrokymography. Hemodynamics and curves of cardiac equilibrium in warm-blooded animals are the interests of Dr. O. F. Ranke at the Physiology Institute in Erlangen and Dr. K. Kramer at the Physiology Institute in Gottingen.

In Cologne much work is being done by such men as Schneider in the perfusion of the brain with blood, Knipping in physiology, Bolt in angiocardiography, and Valentin in pulmonary heart disease. Other German centers of research are Berlin, Wurzburg, Bad Nauheim, Frankfort, and Dusseldorf.

Austria.—Otto Loewi—now at work in Graz—was awarded the Nobel prize for discoveries on chemical transmission of nerve impulses. Philip Knoll, who first worked in Prague and is now in Vienna, is also a distinguished cardiologist. Another scientist of note in Vienna is Kaindl who studies peripheral circulation.

Belgium.—In several scientific centers in Belgium much good cardiac research is being carried on. C. Heymans, in Ghent, a grantee of the National Heart Institute, is a noted cardiac physiologist and received a Nobel prize for his work on the carotid artery. In Brussels, P. Bastenie is a versatile scientist and a clinician. He has made special contributions in the field of hypertension.

Dr. R. Pannier is working in Bruges on mitral stenosis; J. Lambert in Spa, on peripheral circulation; J. Roskam in Liege, on rheumatic fever; and Dr. van Dooren is an eminent cardiologist of Brussels.

Switzerland.—Highly regarded today is Pierre Duchosal of Geneva. He was the first to make vectorcardiography a scientific clinical method.

Another noted clinician and medical scientist is Loffler in Zurich, who has identified some diseases which bear his name. Among others of note are Rothlin, working in the Ciba laboratory in Basel on cardiac drugs, P. H. Rossier and E. Rossi in Zurich, F. Reubi in Berne, and R. Hegglin in St. Gallen.

The Netherlands.—Now working in Amsterdam is I. Boerema, a cardiac surgeon who has suggested modifications of the Blalock and Potts operations. Also D. Durer is carrying on experiments in electrocardiography and serum cholesterol. Vectorcardiography, ballistocardiology, and hemodynamics are prominent among the subjects studied by Professor H. C. Burger, of Utrecht. In Groningen, Dr. J. Nieveen is working on cardiac catheterization, phonocardiography, and various drugs.

Sweden.—Grantee Professor Sune Bergstrom at the University of Lund is investigating the chemical mechanisms of cholesterol, a fatty substance implicated in coronary-artery disease. Also at the University of Lund is Associate Professor Arvid Carlsson, working on the pharmacology of the circulation. Another National Heart Institute grantee is Gustav Nylin at the Cardiovascular Clinic at South Hospital, Stockholm. He is engaged in studies of cerebral blood flow.

At the University of Goteborg in Sweden, Bjorn Folkow is making comparative studies of the physiology of peripheral resistance in normal and hypertensive subjects. In Stockholm, Professor Ulf von Euler is working on hormonal regulation of the circulation, and Dr. F. Lund is studying peripheral circulation. Also in Sweden is Morgens Faber, a biochemist and pathologist who is doing research on aortic atherosclerosis. Gunnar Biorck is an epidemiologist and clinician of note working in Stockholm. Professor C. H. Hjortsjo is conducting embryological studies and research of the bone marrow. He is dean of the Faculty of Medicine at the University of Lund.

Denmark.—In Denmark, among the leading cardiological researchers, is Lindestrom-Lang working in biochemistry. Also at the University of Copenhagen are Walter Falholt and Jorgen Fabricius studying diagnostic techniques, especially dyes used in the detection of congenital heart defects.

Ireland.—Dr. John W. Harman, a grantee of the National Heart Institute at St. Kevin's Hospitals in Dublin, is studying metabolic defects in the blood. O. L. Wade is working in Belfast on pulmonary heart disease.

Russia.—Because of communication difficulties, much of the work being done on cardiology today in Russia is not well known here. Such scientists as L. A. Rybakova, of the Central Institute for Research in Health Education in Moscow, have done extensive work on the role of health education in the prophylaxis of rheumatic fever among children. Dr. Rybakova has devised systems of health education now being used in Moscow health centers and elsewhere in the USSR.

Dr. V. Parin, Scientific Secretary, Academy of Medical Sciences, Moscow, is noted for work on heart physiology.

Also in Moscow is E. M. Leikina, working at the Academy of Medical Science on anticoagulants, more particularly on heparin and on problems of brain hemorrhage caused by nervous trauma. N. V. Bogoyavlenskaya is at the Order of Lenin Central Institute of Hemotology and Blood Transfusion, also studying problems of blood clotting. Further studies of anticoagulants are being made at the Naval Academy at Leningrad by I. A. Sapov, and at the Kuban Medical Institute by V. P. Baluda. L. G. Shikunova is doing research in Moscow on the use of oxygenated blood in resuscitation procedures.

Czechoslovakia.—Two men of note in Prague are Professors J. Brod and Fejfar, both working on management of cardiac insufficiency. Dr. Joseph Charvat of the First Medical Clinic in Prague is well known for his work in internal secretions and atherosclerosis. Professor J. Herles of the Second Medical Clinic in Prague is working on cardio-pulmonary disease.

Poland.—Wiktor Bross, Director of the Institute of Physiology in the Medical Academy of Warsaw, is experimenting with electrical

defibrillating currents in the heart. Professor D. Alexandrof, Chief, Second Medical Clinic of Warsaw, is working on hypertensive heart disease and atherosclerosis.

Spain.—Francisco Vega-Diaz is a contemporary clinical cardiologist of note. He is particularly interested in industrial accidents and diseases, and has a hospital in Madrid specializing in these cases. Another prominent name among Spanish cardiologists is Carlos Jimenez-Diaz who is carrying out research in Madrid on the physiology of blood pressure regulation.

In Barcelona are Juan Gilbert-Queralto, working on cardiac insufficiency, and Fernando Martorell, studying peripheral circulation.

Portugal.—Cardiological research is being carried out in Lisbon by E. Coelho working on acquired vascular diseases, A. Cordeiro studying rheumatic fever, and other researchers such as Ayres de Sousa, J. Cid dos Santos, and J. Moniz de Bettincour.

South Africa.—Two co-investigators, and grantees of the National Heart Institute, who are doing notable work at the University of Capetown, are Drs. B. Bronte-Stewart and J. F. Brock. Their joint study among the Bantu natives concerns the relationship among dietary fat, serum cholesterol, and atherosclerosis. Another grantee, Dr. John Wainwright at the University of Natal is also working on the pathology of atherosclerosis in the Bantus.

India.—S. Padmavati, at the Lady Hardinge Medical College in New Delhi, is a noted epidemiologist and is studying rheumatic fever among the widely variant populations of India.

J. C. Gupta, of the Department of Cardiology at the Institute of Post Graduate Medical Education in Calcutta, formerly at Punjab U., is doing research on the relation of fats to atherosclerosis, and is making comparative studies of the dietary habits in different parts of India. He has also worked on the chemotherapy of hypertension. Another highly regarded scientist in India is Dr. Vakil who is doing research on rauwolfia.

Lebanon.—Surgeon J. L. Wilson, at the American University of Beirut, is working on a National Heart Institute grant for the study of cardiovascular disease in the Middle East, particularly congenital heart disease.

Israel.—The aim of National Heart Institute grantee Franz Sondheimer, working in Rehovoth, is the synthetic preparation of cardiac-active substances from natural products.

Japan.—In Kyoto, cardiac research is being done by Magojiro Maekawa at the University of Kyoto. Haruo Katsunuma, a professor of public health in the Department of Health Care and Nursing at Tokyo University Medical School, is working on the development of health education programs in Japan.

Philippines.—A. A. Camara, a National Heart Institute grantee at the University of Philippines, is doing research on edema.

Australia.—J. K. Maddox is a renowned epidemiologist in Sydney.

New Zealand.—Professor Smirk is working in Dunedin at the Otego University Medical School on ganglionic blocking agents and their use in hypertension.

Canada.—Hans Selye in Montreal (trained in France) is noted for his studies of stress in relationship to coronary heart disease, and for his description of the general adaptation syndrome. He is also a grantee of the National Heart Institute.

Drs. B. Chown and H. H. Gunson, both grantees of the National Heart Institute, are working on the relationship between mother and fetal circulations with particular reference to the Rh factor. Dr. Eleanor Venning, a National Heart Institute grantee at McGill University, is seeking knowledge of the body secretion, aldosterone, and its role in congestive heart failure.

Also Dr. John H. Palmer in Montreal is a noted professor and clinician, and J. D. Keith in Toronto is widely known for his work in rheumatic fever.

Mexico.—One of the outstanding cardiologists of Mexico is Ignacio Chavez. He is a professor of cardiology at the National University of Mexico and is a founder and Director of the National Institute of Cardiology of Mexico.

A. Rosenbleuth is another scientist of note in Mexico, who is working on cardiac electro-physiology. Also in Mexico are such men as D. Sodi-Pallares, E. Cabrera and I. Costero, all noted clinicians and researchers.

Cuba.—A. Castellanos in Havana is working on radiological methods in cardiology.

Colombia.—Two grantees of the National Heart Institute are working independently on atherosclerosis studies among the local population, Dr. E. Lichtenberger and Dr. Carlos Restrepo.

Guatemala.—National Heart Institute grantee Dr. N. S. Scrimshaw at the Institute of Nutrition of Central America and Panama is working on the relationship of atherosclerosis to environmental factors.

Brazil.—In Rio, E. Magalhoes-Gomes is studying subacute bacterial endocarditis. Other well-known names are Dr. Prezzaneze and Menezes.

Argentina.—E. Braun-Menendez, in Buenos Aires, is known for his studies in hypertension. P. Cossio and L. de Saldati are also at work on research into cardiac problems, especially atherosclerosis and cardiac insufficiency.

Peru.—In Lima, A. Rotta is studying heart adaptation.

Chile.—G. Dusaillant of Santiago is doing research on radiological methods in heart disease.

WORLD-WIDE STUDIES

A distinguished study group under the auspices of the World Health Organization is developing a classification with uniform terminology for use in the world-wide study of atherosclerosis. Among the members of this study group are:

Dr. J. A. de Brux, Professeur agrege d'Anatomie pathologique, Chef du Laboratoire d'Anatomie pathologique de l'Hopital Boucicaut, Paris, France (Rapporteur)

Dr. John Higginson, Head, Geographic Pathology Unit, South African Institute for Medical Research, Johannesburg, Union of South Africa

Dr. Toru Miyaji, Professor of Pathology, Osaka University Medical School, Osaka, Japan

Dr. James C. Paterson, Professor of Medical Research, University of Western Ontario, London, Canada (Chairman)

Dr. Carlos Restrepo, Departmento de Patologia, Facultad de Medicina de la Universidad del Valle, Cali, Colombia

Professor A. I. Strukov, Head, Pathological Anatomy Department, Moscow Sechenov Medical Institute, Moscow, U. S. S. R.
Dr. Carlos Tejada, Jefe de la Division de Patologia Clinica, Instituto de Nutricion de Centro America y Panama, Guatemala
Dr. Henry Ungar, Professor of Pathology, Hadassah Medical School, The Hebrew University, Jerusalem, Israel
Dr. P. N. Wahi, Professor of Pathology, Sarojini Naidu Medical College, Agra, India (Vice-Chairman)

Another World Health Organization study group on Atherosclerosis and Ischaemic Heart Disease met in Geneva to discuss the present status of knowledge of these diseases and to advise the WHO on applying this knowledge to further preventive programs. Among the distinguished members of this group are:

Professor J. B. Duguid, Department of Pathology, Royal Victoria Infirmary, Newcastle-upon-Tyne, England
Dr. J. Groen, Wilhelmina Hospital, Amsterdam, Netherlands
Dr. Noboru Kimura, Professor of Medicine, First Medical Clinic, School of Medicine, Kyushu University, Fukuoka, Japan

SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN MICROBIOLOGY

LEEUWENHOEK DISCOVERS MICROORGANISMS

Anton van Leeuwenhoek, a Dutch investigator (1632–1723), first revealed the world of microorganisms (1676). He was a highly intelligent and self-made man who sought to satisfy his restless energy in many areas of knowledge. As one of his avocations, he made minute but powerful lenses and examined a great variety of objects. He examined his own saliva, circulating blood, seminal fluid, urine, and many other materials, and in some of these he was shocked to find living creatures. For the rest of his life, these tiny animals or animalcules, as he called them, claimed his avid interest. He described them and wrote many letters to the Royal Society of London about their appearance and movement. Leeuwenhoek is known as the "father of bacteriology."

DISPUTE OVER ORIGIN OF LIFE

In those days the question of the origin of life caused bitter controversy. For example, it was said that maggots arose spontaneously from a compositional change in decaying meat.

Francesco Redi (1626–1697), an Italian, disputed this. He put meat and fish in glass containers and covered them with gauze. Flies deposited their eggs on the gauze. The meat putrefied, but no maggots appeared; they developed only when the meat itself contained the eggs. It was obvious that maggots were not a transformation of the meat itself. Unfortunately, Redi's work was generally ignored.

About this time, many men surmised that organic matter contained a force for converting itself into new forms of life.

Louis Joblot (1645–1723), a Frenchman, placed hay in water and after a few days saw that his infusion teemed with Leeuwenhoek's animalcules. This seemed to prove spontaneous generation, but Joblot was not satisfied.

He boiled up another batch and separated it into two parts. One he kept sterile by putting it in a carefully baked and closed vessel. The other he left in the open. Nothing happened in the enclosed vessel, but the open one teemed with life in a few days. And so he proved to his own satisfaction that life could not develop from the infusion alone.

NEEDHAM APPARENTLY PROVES SPONTANEOUS GENERATION

An Englishman, *John Needham* (1713–1781), tried similar experiments (1749). Heating both closed and open vessels, he found life in all of them and was certain that spontaneous generation existed. We

know today that he was wrong. He had simply failed to heat his closed vessels long enough. But the argument ran on.

SPALLANZANI DISPROVES NEEDHAM

Spallanzani (1728–1799), a volatile Italian, took up the fight. He kept his vessels tightly closed, heated them long enough, and no animalcules developed (1775). But Needham, with the world on his side, simply shrugged that the heat itself had destroyed the vital force. Spallanzani replied by showing that his closed vessels could still develop animalcules later on out in the air. This closed the argument until Lavoisier discovered oxygen. Then Needham's followers cried out that excluding air from the vessels had prevented life.

EDWARD JENNER INTRODUCES MODERN METHOD OF VACCINATION

One of the most epochal contributions to preventive medicine the world has ever known was made when *Edward Jenner*, an English physician, was impressed by the countryside tradition that milkmaids who contracted cowpox while milking were subsequently immune to smallpox. He vaccinated against smallpox by transferring material from a cowpox pustule on the hand of a milkmaid to the arm of a small boy (1796). Six weeks later the boy was inoculated with smallpox and failed to develop the disease. By 1800 the scientific basis of this method, which is used today, was firmly established.

DISPUTE CONTINUES OVER SPONTANEOUS GENERATION

In 1836 *Schulze* and *Schwann*, Germans, tried passing purified air into the previously heated vessels. This worked and they developed no life. But the opposition sneered that the very way they purified the air destroyed the "life giving" power of oxygen. In 1861 *Schroder* and *von Dusch*, Germans, filtered the air through cotton wool. Again, none of the animalcules appeared, and the argument should have been settled. In spite of all this, few were convinced until the magnificent Pasteur showed that the microorganisms in the air were caught by the cotton wool.

SEMMELWEIS SHOWS HOW TO PREVENT PUERPERAL FEVER

The Austrian, *Semmelweis*, noted that the death rate of women at childbirth was higher in certain clinics where the medical students and physicians came directly to the wards from the morgue or gross dissection room. Making other observations, he concluded rightly that puerperal fever was an infectious disease (1861). On his own wards he forced physicians to clean their hands scrupulously before examining patients and the mortality dropped immediately. Unfortunately, his views as to the nature of puerperal fever met with strong opposition and were not accepted for 20 years after his death.

PASTEUR DEVISES PASTEURIZATION

Louis Pasteur (1822–1895) is perhaps the greatest French scientist of all time. A very patriotic man, many of his greatest discoveries

grew out of his deep devotion to his beloved France. Told by an Englishman that French wines were not popular in England because they soured, he set out to discover why. At first he studied beer, a special subject for him, since Germany made a better beer at the time. As a result of his experiments, he showed that living microorganisms caused fermentation and putrefaction. His answer was to heat both wine and beer—that is, to pasteurize them and kill the organisms (1867). Pasteur did not miss the implication of his work, for he later wrote: "When we see beer and wine subjected to deep alterations introduced and now swarming within them, it is impossible not to be pursued by the thought that similar facts may, must, take place in animals and in man!" This was a profound thought—that germs caused disease in man. In 1885 Pasteur developed his treatment for rabies. His method, but slightly modified, is used throughout the world today.

LORD LISTER APPLIES ANTISEPTIC TREATMENT TO PREVENT WOUND INFECTION

Lord Lister (1827-1912), a great English surgeon, applied the basic ideas of Pasteur to surgery. To prevent infection during an operation, he began to operate in a spray of carbolic acid (1875). His methods were not too satisfactory, but our modern aseptic techniques grew out of it. Lister is known as the "father of antiseptic surgery."

KOCH ISOLATES ANTHRAX BACILLUS IN PURE CULTURE

Robert Koch (1843-1910), a German, made bacteriology an exact science. As an obscure physician in Wollstein, Silesia, he tracked down the microorganism in the blood of animals dead in a local epidemic of anthrax. He bred this germ in a pure culture and found he could infect other animals with it (1876). His discovery that specific germs cause specific diseases was one of the most epoch-making in all the history of medicine. Out of this basic fact, the microbes of gonorrhea, diphtheria, typhoid fever, gangrene, and many other diseases were quickly discovered. Koch, himself, isolated tuberculosis and cholera germs. He was given the Nobel Prize in 1905.

LAVERAN DISCOVERS PARASITE OF MALARIA

Alphonse Charles Louis Laveran (1845-1922), a Frenchman, found microscopic bodies in the red blood cells of malarial patients in 1880. After checking the various stages through which the parasite passed, he theorized that the mosquito played a part in malaria transmission.

Although Laveran did not get immediate recognition for his discovery of the malaria parasite, his findings were soon confirmed and extended. He and other workers now could observe the parasites' association with the characteristic malaria pigment and their disappearance after quinine treatment. These were indeed the long-sought malaria "germs." Laveran received the Nobel Prize in 1907.

METCHNIKOFF ANNOUNCES THEORY OF IMMUNITY

Eli Metchnikoff (1845-1916) was born in the province of *Kharkov, Russia.* The son of an officer of the Imperial Guard, he was privately

tutored in childhood and later took a degree at the University of Kharkov. While occupied with experimental work on the origin of the digestive organs, it struck him that certain organisms having no part in the digestion of food are nevertheless capable of engulfing foreign bodies. He switched his attention to this puzzle and in a brilliant series of experiments showed that these organisms—while blood cells—destroyed bacteria. He called them the body's first line of defense against disease. This discovery and its relationship to antibodies is the foundation of the science of immunology (1882). Metchnikoff received the Nobel Prize in 1908.

GRAM INTRODUCES HIS METHOD OF STAINING BACTERIA

Christian Gram, a Danish physician, introduced the very important method of differential staining known as Gram's method (1884). After an initial staining, Gram used an iodine solution followed by alcohol. He noted that certain bacteria retain the initial color when treated with alcohol, whereas others do not. Gram's method remains essentially unaltered today as one of the first steps in classifying bacteria.

KITASATO CULTIVATES THE TETANUS BACILLUS

Shibasaburo Kitasato, a Japanese, was a pupil and colleague of Koch. He was unable to find the tetanus bacillus in animals that had died of the disease, but felt the disease process to be the result of an intoxication rather than of bacterial invasion. He cultivated the tetanus bacillus in 1889.

VON BEHRING AND KITASATO DISCOVER TETANUS ANTITOXIN; VON BEHRING DISCOVERS DIPHTHERIA ANTITOXIN

Kitasato and *Emil von Behring*, a German (1854–1917), also an assistant in Koch's laboratory, found that experimental animals treated with tetanus toxin developed a transferable immunity (1890). Kitasato and von Behring published their results and in a footnote the word "antitoxin" became firmly established. A week after he announced the discovery of tetanus antitoxin, von Behring published an article on immunization against diphtheria. The discovery of the toxin-antitoxin relationship was very important in the development of the science of immunology.

IWANOWSKI DISCOVERS FIRST VIRUS

Iwanowski, a Russian, reported experiments which led to an understanding of the viruses (1892). This first virus was the tobacco mosaic virus. Iwanowski's work was repeated and extended in 1898 by *Beijerinck*. In addition to being the first virus discovered, the virus of tobacco mosaic was the first to be purified in a crystalline form. This was done by an American, *Dr. Wendell M. Stanley*, in 1935.

KARL LANDSTEINER DISCOVERS THE BLOOD GROUPS

Karl Landsteiner, an Austrian scientist, came to America and held an important post with the Rockefeller Institute of Medical Research in New York. He found that normal human blood falls into four

main groups, the blood of some of these groups capable of destroying blood belonging to other groups (1900–1912). This laid the foundation for modern blood transfusion. In 1940 Landsteiner and Wiener identified the Rh factor in blood.

EHRLICH INTRODUCES METHODS OF STANDARDIZING TOXINS AND ANTITOXINS

Paul Ehrlich, a German (1854–1915), outstanding scientist and genius of extraordinary activity, added a great mass to our knowledge of medical science. He applied stains to cells and tissues for purposes of revealing their function (1896). He founded and was the greatest exponent of the science of hematology. In 1897, he announced the "side-chain" theory of immunity. Ehrlich conceived protein molecules to be similar to a benzene ring with unstable side chains. These could act as chemoreceptors to combine with harmful materials to neutralize them. This theory, although not entirely applicable, has never been completely discarded. In 1910 he introduced Salvarsan as a treatment for syphilis, and thus played a significant part in the creation of the new branch of medicine known as chemotherapy.

ROSS DISCOVERS HOW MALARIA IS TRANSMITTED

Sir Ronald Ross (1857–1932) was born in Nepal of an Anglo-Indian family. He studied bacteriology in London and, on returning to India, became interested in the way malaria is transmitted. In 1897, while dissecting an anopheles mosquito, he discovered the malarial parasite in the walls of its stomach (1897). He was the first to demonstrate the life cycle of the parasite, using malaria infections in birds. While his early hopes that his work would lead to the eradication of the disease have not been fully realized, it laid the groundwork for systematic study of the disease and mosquito control programs. Ross received the Nobel Prize in 1902.

GRASSI SHOWS HOW MALARIA IS TRANSMITTED IN HUMANS

Giovanni Battista Grassi, an Italian (1854–1925), was born near Lake Como, graduated in medicine at Pavia, and appointed professor of anatomy at the University of Rome. In his earlier years he did important work on the parasites of man and animals. In September of 1898 Grassi collected anopheles mosquitoes in a malarious area of Italy and took them to the Santo Spirito hospital in Rome, where he allowed them to feed on volunteers. They promptly came down with the disease, completing his proof of the method of man's infection (1898).

MICALLE LINKS BODY LOUSE WITH TYPHUS TRANSMISSION

Charles Micalle (1866–1936) learned his medicine in Paris. He became director of the Pasteur Institute, where he began to investigate typhus. While there he noticed that even though typhus patients were lodged in a common ward, no other patients caught the disease. Yet their families, and the hospital admitting personnel who relieved

them of their clothing, caught it. He reasoned that the disease agent was something attached to the skin or to the patient's linen—something which soap and water got rid of. This could only be the louse. Later he verified his hypothesis by reproducing the malady in animals (1902). Micalle was awarded the Nobel Prize in 1928.

HOWARD T. RICKETTS OBSERVES RICKETTSIAE

Howard T. Ricketts, an American, demonstrated that Rocky Mountain spotted fever was transmitted by the wood tick (1909). Several years later he showed that Mexican typhus was transmitted by the body louse, but in the investigation he contracted the disease and died of it. His name has been given to the whole group of similar organisms known as the rickettsiae.

VON BEHRING FIRST USES TOXIN-ANTITOXIN

In the same year that von Behring first used toxin-antitoxin mixtures to produce a permanent and active immunity, *Bela Schick*, an Austrian pediatrician, introduced a skin test for susceptibility to diphtheria—the Schick test (1913). This was followed by the development of many other diagnostic skin tests.

SIR ALEXANDER FLEMING DISCOVERS PENICILLIN

Returning from a week's vacation, *Alexander Fleming*, a Scotchman, peered curiously at staph organisms inhibited by a chance streak of contaminating mold. He extracted the inhibitory material from the mold and named it penicillin (1929). Without concentration, however, penicillin was useless in combatting diseases in man. And it was not until 1941, when *Ernst B. Chain* and *Howard W. Florey*, Englishmen, overcame the difficulties involved and demonstrated its therapeutic powers, that its full potential was realized. Penicillin was at that time the most powerful microbe killer ever discovered, and today it remains the most important of the antibiotic drugs. Fleming, Chain, and Florey received the Nobel Prize in 1945.

GERHARD DOMAGK DISCOVERS PRONTOSIL, THE FORERUNNER OF THE SULFA DRUGS

Gerhard Domagk, a German, entered the University of Kiel just as World War I broke out. He volunteered for the Army and returned to graduate after the war. While working for the I. G. Farbenindustrie in the thirties, it was his job to test the therapeutic effects of the chemicals produced. In this way he discovered the extraordinary powers of the sulfonamide drugs (1935). Although the antibiotics are now more prominent in treating diseases, the sulfonamides are still widely used. They are cheap and effective; and prior to penicillin, they revolutionized the management of many important diseases.

When Domagk received the Nobel Prize in 1939 he sent a letter of thanks. In the following month, because of the Gestapo, he sent a second letter repudiating the prize. It was not until 1947 that he delivered his Nobel lecture and received the gold medal—too late, however, for the award of prize money.

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WAKSMAN DISCOVERS STREPTOMYCIN

The development of streptomycin came as the result of a planned, careful search for an antibiotic agent effective against certain kinds of bacteria. Within a period of five years, nearly ten thousand cultures were examined before streptomycin was found (1940) by *S. A. Waksman*, a Russian-born microbiologist, at Rutgers University. Within less than a year, it was shown to be effective against certain forms of human tuberculosis, and so, for the first time in history a drug was found which could be used for its treatment.

In recent years microbiological medicine has continued to grow. *C. H. Andrews* and other Englishmen first isolated the human influenza virus in 1933. Andrews is now directing important research on the common cold.

In 1949 the Americans Enders, Robbins, and Weller showed how to cultivate poliomyelitis virus in monkey tissues in flasks. This provided the basic observation from which polio vaccine was later made. *Sir MacFarlane Burnett*, an Australian, has become one of the prime movers in basic research on host-cell virus relationship. *Lwoff*, a Frenchman, at the Pasteur Institute leads a group studying the reproduction of virus. *Tiselius*, a Swede, is doing vital work on electrophoresis for various types of proteins.

Smorodinstef and *Zdanoff*, Russians, can be singled out for their work on the serological relationship between viral encephalomyelitis and multiple sclerosis. And *Chumakov*, another Russian, conducted important studies on the various aspects of influenza, including the development of an intranasal spray for its prevention.

SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN THE FIELD OF ARTHRITIS AND METABOLIC DISEASES

The National Institute of Arthritis and Metabolic Diseases, having its origin in several of the oldest research laboratories of the Public Health Service, has maintained interest and activity in a large number of disease areas of medicine. This broad interest is reflected in the title of NIAMD's immediate antecedent, the Experimental Biology and Medicine Institute. The disease areas of present principal concern are the following: diabetes mellitus, arthritis and related rheumatic or collagen diseases, diseases of nutrition and metabolism, diseases of the endocrine glands (thyroid, parathyroid, adrenal), diseases of the blood, and disorders of the gastrointestinal tract.

A majority of the outstanding scientific contributions and accomplishments in these fields up through the nineteenth century came from European physicians, chemists, and physiologists. With the development of the Hopkins system of medical education in 1890, however, and the gradually improving training of young American physicians in scientific methods of medical research, American contributions steadily increased and are now predominant in the expanding attack on disease. Also during the past fifty years, American chemists and biologists have more frequently produced fundamental advances of value to medicine, although an impressive number of important contributions continue to come from foreign scientists.

DIABETES

Scientific definition and understanding of the complex disorder of carbohydrate metabolism known as diabetes mellitus began during the 17th century in England when Dr. Robert Willis, friend of Isaac Newton and Christopher Wren, first reported the sweet taste of the urine of diabetic patients and thereby differentiated diabetes mellitus, "sugar diabetes," from diabetes insipidus, or "water diabetes." Patients with the latter disease also pass large volumes of urine, but do so as the result of a specific lesion in the posterior lobe of the pituitary gland, and their urine does not contain sugar.

In mid-19th century Claude Bernard of Paris discovered glycogen, the principal storage form of sugars (in the liver and in muscle), and recognized this material as a source of the sugar of the blood. Within the past few years in NIAMD laboratories, Drs. DeWitt and Marjorie Stetten have added greatly to our knowledge of the forms and mechanisms of storage and release of glycogen.

During the hey-day of descriptive medicine, Adolf Kussmaul, a German, in 1874 not only delineated the classic breathing of the patient in diabetic coma, but related the forceful respirations to the body's need to extrude toxic acidic substances produced during severe alteration of the processes of burning and storage of sugar.

An extremely important landmark in diabetic progress was reached in 1890 when definite association between the pancreas and diabetes was shown by the Germans, Oskar Minkowski and Joseph von Mehring. They found that when the pancreas was removed from dogs, permanent diabetes resulted, corresponding to a severe form of this disease in man. Another German, Paul Langerhans, studied the microanatomy of the pancreas and recognized the small islets of tissue now named after him. Several investigators by the first decade of the 20th century obtained evidence suggesting the islets to be the sites of insulin production. A vigorous race to isolate insulin ensued, which was won in 1921 by the Canadians Sir Frederick Banting and Charles Best.

Use of insulin in the treatment of diabetes followed rapidly upon the development, largely by American pharmaceutical firms, of methods for its industrial production. Insulin was obtained as a pure crystalline protein by an American, John Abel, at Johns Hopkins in 1926. English workers at Cambridge, Sanger and his associates, then established its chemical structure, the first protein for which a complete chemical formula could be written. As an important means of reaching more rapidly the day of better and simpler control and ultimate understanding of diabetes, investigators are now engaged in the rigorous work of determining the precise spatial and bonding configurations of insulin structure which are responsible for its action on sugar in the body.

Coincident with the effort to isolate insulin and evaluate its action, extensive studies have been made of the fundamental processes of metabolism by which glucose is utilized in the body controlled by the catalysts known as enzymes. The contributions of Warburg and Meyerhof in Germany (from 1920 on) have been pre-eminent in formulation of these important metabolic pathways, as have also the studies of Carl and Gerty Cori, Austrians working in this country. Extension of basic carbohydrate metabolism studies has been an important part of NIAMD's activities in this field.

Another extremely important aspect of diabetic research, particularly during the past 30 years, has been the physiological approach. Physiological studies endeavor to elucidate the regulation of carbohydrate and fat metabolism by the complex interplay between the secretions of the anterior pituitary, the adrenal cortical hormones, and in some instances the hormone of the adrenal medulla. Foremost in these at once competitive and collaborative endeavors have been Bernardo Houssay of Argentina, F. G. Young of England, and in this country, C. N. H. Long (English), W. C. Stadie, Richard de Bodo (Hungarian) and Rachmiel Levine; the latter is particularly noteworthy because of his elucidation (1950) of the primary mechanism by which the hormone insulin exerts its action (by increasing the permeability of membranes to various sugars). The investigations of these several scientists have in various ways contributed greatly toward understanding of the disturbance in hormonal balance thought to exist in diabetes.

THE RHEUMATIC DISEASES

The rheumatic diseases comprise a number of clinical disorders of the joints and connective tissues of the body. Rheumatoid arthritis, rheumatic fever, osteoarthritis, gout, spondylitis, disseminated lupus

erythematosus, polyarteritis, and scleroderma are the principal members of this group. These disabling afflictions are among the oldest of known diseases; prehistoric skeletons disinterred in Egypt, for example, have shown some of the deformities of rheumatoid arthritis. In ancient Greek times the physician Alexander of Tralles (525–605 A. D.) prescribed colchicine for gout, and this drug is still the sovereign therapeutic agent for this disease.

Up to the beginning of the 20th century, principal advances were made in the difficult task of unraveling the complex clinical characteristics of these various diseases. English physicians showed the greatest aptitude in this respect, as Thomas Sydenham in 1676 gave the first full description of acute rheumatic fever and in 1683 distinguished between it and gout. David Pitcairn (1788) was the first to associate rheumatism with the heart, and Scudamore in 1827 asserted that the true pathology of chronic rheumatism was an inflammation of the white fibrous tissues of the body (ligaments and tendons) and not the fleshy parts of muscle. A most important step in gout was the recognition in 1848 by A. B. Garrod that the tophi of this disease consist of uric acid crystals and his demonstration by means of a thread that the blood of gouty patients contains an excess of uric acid. This English physician also coined the term "rheumatoid arthritis," and his son, A. E. Garrod, in 1907 distinguished correctly and clearly between rheumatoid arthritis and osteoarthritis. The first accurate description of spondylitis, on the other hand, was the early (17th century) contribution of an Irishman, Bernard Connor. The distinctive microscopic lesion in heart muscle which identifies rheumatic heart disease was made by a German, Aschoff, in 1904.

Among the less common collagen diseases, lupus erythematosus was recognized in 1872 as a systemic disease and not simply a skin disorder by Kaposi, an Austrian, and the complications within various organs of the body were described by Osler, a Canadian, a few years later (1895) while at Hopkins. The means of making a virtually specific pathologic confirmation of a clinical diagnosis was provided in 1935 by Baehr and Klemperer (American and German) who described "wire loop" kidney lesions. An American, Hargraves, in 1948 made an important contribution to clinical laboratory diagnosis by discovering a distinctive cell in the circulating blood.

Clinical and pathologic descriptions of polyarteritis go back nearly 200 years, but the Germans, Rokitansky (1852) and Kussmaul (1866), are given credit for the most appropriate delineations of the distinctive arterial lesions of this disease. The suggestion that polyarteritis is due to an allergic or hypersensitivity phenomenon was suggested by a German, Gruber, in 1925, but classical demonstration that the typical lesions could be experimentally produced by a hypersensivity reaction was made by the American pathologist, Rich, in 1942. The disease, scleroderma, was apparently earliest described during the 17th and 18th centuries by Italian and Dutch physicians. Recognition that the hardening process of this disorder was not limited to the skin was made variously by an Englishman, Finlay, in 1891, who noted fibrosis of the lungs, by Ehrman, an Austrian, in 1903, who found thickening of the esophagus, and by an American, Rake, who in 1931 noted involvement of the intestine.

The past 20 years has seen an intensification of interest in the rheumatic diseases and the application of varied and sophisticated research techniques. These latter have been directed toward fundamental studies of connective tissue structure and metabolism, the relationship of infectious agents, investigation of hypersensitivity mechanisms, and study of the influence of endocrine hormones. In rheumatic fever more definite progress has been made than in the other connective tissue diseases. The suppressive action of salicylates on acute attacks was noted at least as early as the nineteenth century by various European physicians; involvement of the hemolytic streptococcus was suspected by German investigators at the end of the last century, but laboratory evidence for its close association was obtained by Coburn (1931) and other Americans; the prophylactic value of antibiotics on the recurrence of the disease has been observed (Thomas, Coburn, and other Americans, 1939); and the therapeutic efficacy of adrenal cortical steroids realized (Hench and others, 1949). The most stimulating recent contribution in the field has been the striking effect of cortisone (Hench and Kendall, 1948, Mayo Clinic) on the acute symptoms of rheumatoid arthritis. American pharmaceutical firms are now industriously synthesizing various modifications of the adrenal cortical steroid molecule (being tested clinically and in animals in various American medical centers) in the effort to obtain a more effective, less toxic therapeutic agent. Other important developments in rheumatoid arthritis during this century have been the introduction of gold salt therapy in 1927 by Lande and Pick (Germans) and in 1929 by Forestier (French); a significant advance in serological testing for the disease by Waaler, a Norwegian, in 1940, who first employed sensitized sheep cells for agglutination; and definition of vasculitis as the important pathogenetic lesion in the subcutaneous nodule (1953, Sokoloff, an American now at NIAMD, NIH).

NUTRITION AND METABOLISM

The science of nutrition and metabolism owes its inception and early development mainly to contributions during the 18th and 19th centuries, first from the English and French and later from the Germans. Discovery of oxygen, the "fire air" or air of life is generally attributed to the Englishman, Priestley, who was in communication with Lavoisier and Seguin in Paris. The latter investigators in approximately 1790 made a key experiment (both the heat and the carbon dioxide produced by a guinea pig in a given time were found equivalent to the heat and the carbon dioxide produced by burning a specific quantity of carbon) which demonstrated the significance of the respiratory process in relation to the utilization of food for energy. Extension of these studies to man with further understanding of the metabolic processes by which food is burned in oxygen to yield energy for life and growth were carried out by the French, Regnault and Reiset, and by the Germans, Liebig (divided foods into proteins, fat, and carbohydrates), Bidder and Schmidt (established basal metabolism), Pettenkofer, Voit, and Rubner (demonstrated physical law of conservation of energy in the animal body). Respiratory metabolism studies were then largely carried forward in this country, by Atwater, Benedict, Lusk, and Dubois, mainly during the first 30 years of this century, and are now with modern dynamic tech-

niques being pushed forward again in a very few centers, including NIAMD in NIH.

Knowledge of the metabolism of proteins was advanced particularly by the German, Emil Fischer, who at the end of the 19th century devised quantitative methods for isolating amino acids and showed specificity of enzyme action, and by Folin (Swedish, 1912) and Van-Slyke (American, 1913) who studied the breakdown metabolic processes of proteins. In 1937, the American, W. C. Rose, demonstrated the thesis that there are 10 amino acids essential for the building of body protein. Advances in carbohydrate metabolism owe much to the Germans, Fischer, Embden, and Meyerhof, at the turn of the century (pathways of metabolism), to the Englishman Cathcart (1909, protein-sparing action) and to others mentioned in the diabetes section. Studies of the metabolism of fat have been principally conducted since 1900. Liebig (German) showed fat synthesis from carbohydrates; Lebedev (1882, Russian) found that dietary fats could be deposited in the body; Knoop (1905, German) determined the chief process of breakdown, or catabolism; and Lusk (1922, American) studied fat synthesis from protein.

The importance of the accessory dietary substances now known as vitamins first began to be appreciated with the discovery in 1747 by the British naval surgeon Lind that citrus fruits were effective preventives of scurvy. Isolation and identification of vitamin C, however, the factor whose absence is responsible for this disease, was not made until 1932 when it was crystallized by Americans, Waugh and C. G. King (the latter at present a member of NIAMD's National Advisory Council). First experimental evidence that accessory food factors were essential, representing the true beginning of vitamin research, came from Lunin in the Swiss laboratory of Bunge who in 1884 showed that there was a growth factor in natural milk not present in synthetic milk. The chemical constitution of this factor, vitamin A, was finally determined in 1933 by Karrer of Switzerland, although much of the early work leading to this achievement was carried out at Yale and Wisconsin Universities, and crystallization was achieved by an American, Holmes, in 1934. In the treatment of rickets, a Russian, Schabad, in 1909, was apparently the first to appreciate cod liver oil as being more important than minerals; isolation of an anti-rachitic substance named vitamin D was made in 1920 by both British and American workers, the preparation of a highly concentrated substance being made by Zucker, an American, in 1921. Recognition of beri-beri as a dietary disease was made (1883) by a Japanese naval medical officer, Takaki. Vitamin B_1 or thiamine, which cures beri-beri, was first crystallized in 1926 by Jansen and Donath in Amsterdam, but earlier the preparation of an impure concentrate in 1911 by Casimir Funk, a Pole working in London, prompted him to coin the term "vitamin" for those dietary factors which we now recognize as being required in very small amounts. Lohman and Schuster (Germans) showed that thiamine is a co-factor for an important enzyme system involved in the metabolism of carbohydrate.

Other members of the "vitamin B complex" have been even more difficult to track down. The recognition of niacin as a cure for pellagra stems from the work of Goldberger (American, U. S. Public Health Service, 1925), who showed that the disease is not infectious

but of nutritional origin. Spencer, a veterinarian in North Carolina, recognized (1916) that the condition called "black tongue" in the dogs of the pellagrins was the counterpart of the human disease. This observation led in 1938 to the isolation of niacin as a cure for the condition by Elvehjem and co-workers at Wisconsin. Simultaneous work by von Euler in Sweden and Warburg and Christian in Germany showed that niacin was a part of the co-factors required by the enzymes which regulate many of the biochemical reactions leading to the production of energy.

Since dermatitis was such a prominent symptom in pellagra, it was inevitable that many skin conditions produced in animals by dietary means should have been considered related to pellagra. For a number of years "rat dermatitis" was in this category until it was shown by Booher (American, 1931) that the rats could be cured by a yellowish-green pigment which was shown by Kuhn (German, 1933) to be riboflavin. This pigment was described in 1879 by Blyth, an English food chemist. In 1932 Warburg and Christian (Germans) showed that the yellow pigment was an essential part of a new enzyme shown by them to be involved in the oxidation of foodstuffs.

Additional work on rat "pellagra", also produced by dietary means, led Gyorgy in 1936 (German) to suggest that a new factor was required for its prevention. This compound, pyridoxine, was isolated by Keresztesy (NIAMD) and Stevens in 1939, and is now recognized as an important constituent of a number of enzymes required for the metabolism of proteins.

Wildiers, a Belgian botanist, found that a strain of yeast would not grow unless a yeast extract was added to a medium of inorganic salt and sugar. An extension of this work by Williams at Oregon resulted in the isolation in 1937 of pantothenic acid. Jukes at California and Wooleys at Wisconsin showed that this substance was essential for the growth of chicks. F. Lipmann (a German refugee in the U. S.) showed that pantothenic acid is a constituent of a co-factor involved in many important biological reactions.

A new and increasingly important segment of the area of metabolism and metabolic diseases is that of disorders due to enzymatic defects known as "molecular diseases." The accomplishments to date have all been made in American laboratories but by individuals of various national extractions. The first such disease, sickle cell anemia, was unraveled in 1953 due to the manufacture of an abnormal hemoglobin by Itano working in Linus Pauling's laboratory at the California Institute of Technology. The next, galactosemia, was resolved as due to the lack of an enzyme required to metabolize milk sugar by Isselbacher working at NIH (NIAMD) with Tomkins and Kalckar, a Dane. The most recent such disease, congenital nonhemolytic jaundice, yielded to the joint efforts of R. Schmid, a Swiss, and J. Axelrod, an American, at NIH (NIAMD and NIMH), who detected the absence of a key enzyme necessary for conversion of bile pigment to the form in which it can be excreted by the liver.

ENDOCRINE DISEASES

Delineation of the diseases of the endocrine glands began in 1855 with the description by Thomas Addison of England of the symptoms and signs of hypoadrenalism now generally called Addison's disease.

Confirmation of the accuracy of Addison's assignment of their cause was provided in 1856 by a Frenchman, Brown-Sequard, who excised the adrenal glands of animals and reproduced the disease. The various physiological studies of Claude Bernard on the liver and pancreas also were begun about this same time. With Berthollet, a chemist of Paris, Bernard introduced the science of biochemistry in unraveling the nature of the first carefully studied enzyme, lipase of the pancreas which is excreted into the intestine. The science of endocrinology, or study of the internal secretions of endocrine glands, became firmly established at the turn of the century with the discovery by Williams Bayliss and Ernest Starling that secretion of pancreatic juice into the intestine did not occur from a neural reflex but from the action of a substance called secretin put out by intestinal lining cells under the influence of acid and carried in the blood stream to the pancreatic glands. These two British investigators coined the word "hormone" or chemical messenger, for a substance passing from an endocrine gland through the circulation to some distant organ or tissue where it exerts its stimulatory or regulatory effect.

The classic diseases of the thyroid gland, hyperthyroidism and myxedema or hypothyroidism, were described during the late 18th and early 19th century by various English physicians. Not until 1882, however, was surgical removal of the thyroid gland directly related to myxedema; this was noted by two Swiss physicians, Reverdin and Kocher, and led to their treatment of this disease by administration of thyroid extract. The association of iodine with activity of the thyroid is credited to Eugen Baumann, a German, who in 1896 discovered its high concentration in the gland, although the first report of therapeutic benefit of iodine on goiter was made in 1820 by a French physician, Coindet. Americans, Marine and Kimball, in 1918 reported their classic study of the prophylactic effect on goiter incidence of daily ingestion of small amounts of iodine, leading the way to iodization of table salt. The nature of the thyroid hormone seemed established in 1915 when E. C. Kendall at the Mayo Foundation crystallized 1–thyroxine from thyroid tissue, and its chemical structure was elucidated by Harington, an Englishman, in 1926. Within the past five years, however, the question of the nature of the thyroid hormone acting on tissues and cells of the body has been reopened by the work of the British investigators, Gross and Pitt-Rivers, and by the Frenchman, Roche, and is still unsettled.

Because of their small size and intimate anatomical association with the thyroid, the parathyroid glands were not identified and associated with the clinical entity, tetany, until the very end of the 19th century by Gley of France and Vassale and Generali of Italy. Halsted, the famous Hopkins surgeon, treated (1906) tetany successfully with beef parathyroid. The association of calcium metabolism with the parathyroids in 1908 by treatment of tetany with calcium, was also an American contribution (MacCallum and Voegtlin). Recognition of the fact that skeletal demineralization can be due to over-secretion of parathyroid hormone was made in 1925 by Felix Mandl of Vienna, who then carried out the first surgical removal of a functioning parathyroid glandular tumor. In a Canadian laboratory in 1926, J. B. Collip isolated what was then considered to be the parathyroid hormone; in recent years evidence for two distinct actions (on the kidney

originally by Greenwald in 1925 and directly on bone by Barnicot in 1948) have led to the effort, primarily in this country, to isolate two parathyroid hormones.

The story of the adrenal glands, now claiming such considerable attention, began with the description of the disease occurring with their hypofunction in human beings (Addison, English, 1855) and with their excision in animals (Brown-Sequard, French, 1856). The next landmark was the isolation of the hormone adrenaline from the adrenal medulla apparently independently in 1901 by an American, Aldrich, and a Japanese, Takamine. Emphasis has since shifted to the adrenal cortex because of its numerous important hormones. Potent extracts were prepared by several investigators during the 1920's; and during the 1930's in American and Swiss laboratories, 28 crystalline adrenal cortical hormones were isolated in small amounts from the glands of animals. Real progress in physiological research in this area, however, had to await the production of hormones in quantity by chemical synthesis; the first effective step in this direction was the preparation in 1937 by the Swiss investigators, Steiger and Reichstein, of desoxycorticosterone, found to be effective against clinical Addison's disease. The next accomplishment, which was even more significant, was made by E. C. Kendall at the Mayo Clinic in 1948 with the synthesis of compound E (cortisone), which was then given by Hench to patients with rheumatoid arthritis with strikingly effective results. The adrenal steroid of greatest interest today is the salt-regulating hormone, aldosterone, whose isolation was achieved in 1954 through the collaborative efforts of Simpson and Tait in England and Reichstein in Switzerland. American investigators have made their particular contributions in this field in numerous physiological studies of the actions and varying influences of other substances on a number of the adrenal cortical hormones.

DISEASES OF THE BLOOD

Establishment of the field of hematology on a sound, scientific basis by the beginning of this century was primarily the work of the French and the Germans, but the initial step was made by a Dutchman, Anton van Leeuwenhoek, who in approximately 1660 invented the microscope and, among many objects, described the red blood cells of man. This instrument was long generally regarded as merely an amusing toy, so that not until nearly 200 years later was the first blood count made (Vierordt, German, 1852). Two famous names in hematology, the Frenchman, Georges Hayem and the Austrian, Wilhelm Turk, then provided the diluting solutions still used by laboratories today for counting red and white cells. The study of blood chemistry was initiated by Gabriel Andral (French) in 1843 with quantitative measurements of the clotting essential, fibrin. Real understanding of both normal and diseased hematological processes occurred when in 1868 the German, E. Neumann and the Italian, Giulio Bizzozero simultaneously reported evidence for the blood formation function of the bone marrow; understanding of these processes was further aided by Paul Ehrlich's discovery in 1891 of methods for colorful staining and identification of blood cells.

The disease chronic congenital hemolytic jaundice was described variously during the 19th century, but it required application of the

osmotic fragility test by Anatole Chauffard (French, 1907) to differentiate the jaundice from that due to liver disease by showing the increased susceptibility of red cells in this blood disease to lysis in dilute saline. Earlier (1871) the Belgians, Vanlair and Masius, contributed precise descriptions of the characteristic tiny rounded cells (spherocytes) in this disease. The acquired form of this hemolytic jaundice, due to infections or poisons, was described in 1898 and 1907 by the French, Hayem and Fernand Widal.

Blood transfusions are today probably the most important form of hematologic therapy. Although the first transfusion of blood to a human patient was given in 1818 by James Blondell in London, a firm scientific basis for safe transfusions was provided in 1901 by an Austrian, Landsteiner, who described the major human blood types or groups. Improved methods of blood transfusion were the work of men of many nations (United States, England, France), given impetus by the first World War. It was found at this time, for example, that blood could be prevented from clotting and stored for long periods, thus greatly simplifying transfusion procedure.

Understanding of the specific hematologic diseases, pernicious anemia and hemorrhagic disease of the new-born, came as the result of unraveling their relationships to vitamin deficiencies. The Americans, Minot, Murphy, and Whipple, in the thirties found pernicious anemia to be due to lack of a factor in liver. Ultimately vitamin B-12 was found to be the missing substance in these patients. Study of a hemorrhagic disorder in cattle occurring when they were fed spoiled clover led to the finding of vitamin K by Link (United States, 1940) and of its importance in blood coagulation. Important basic studies of blood coagulation were contributed during the thirties by Wolf (Belgian) and Howell (American).

Important recent advances, of great importance to transfusion therapy and anemias of the new-born, have been made during the forties by Fisher (England) and Weiner (United States) who have defined new substances related to the Rh factor. The concept of immunologic disorders as the cause of anemias and deficiencies of other important blood cells has recently been established by Evans in America, Ackroyd in England, and Moeschlein in Switzerland.

GASTROINTESTINAL DISEASES

The first important work in the physiology of digestion occurred during the 18th century when the Italian, Spallanzani, correctly characterized the action of gastric juice as chemical solution. One of the classics of clinical physiological investigation was produced by the American Army surgeon, William Beaumont; in his study of the open stomach wound of a forest guide (1825-33), Beaumont directly observed the action of the stomach lining during disgestion and concluded that in the action of gastric juice on proteins a substance other than hydrochloric acid must be present, an agent later identified as the enzyme, pepsin.

Stomach tubes, first of metal and later of a flexible material, were used from the 16th century on for feeding patients in various diseases, but two Germans devised important new uses; Kussmaul in 1867 used the tube as a pump to relieve obstruction and Leube in 1871 began its use for diagnostic examination of gastric secretion, of particularly

valuable later use for aiding in the diagnosis of ulcers and cancer of the stomach.

The most important advance, however, in gastroenterologic diagnosis stemmed from the discovery of the X-ray in 1895 by the German physicist, Roentgen. The first visualization of the stomach by X-ray was apparently made by an American, Hemmeter, and the first experimental roentgenographic observations of swallowing and intestinal movements by the American physiologist, Walter B. Cannon, in 1897. The modern opaque medium, barium sulfate, was introduced by the Germans, Bachem and Gunther, in 1910. Gall bladder X-ray visualization was an American contribution (Graham and Cole, 1924).

The talented Kussmaul attempted in 1869 the first direct observation of the stomach by passing a straight metal tube down the esophagus. Gradually better tubes were devised but the instrument of von Mikulicz-Radecke (1881) was so far superior that he is regarded as the founder of gastroscopy. More recent efforts in gastroenterology, predominantly in American centers, have been directed mainly toward increasing knowledge of the physiology of the intestinal tract, particularly with respect to motility.

In view of the orientation of this account toward research accomplishments, a catalogue of the physicians first to describe the numerous gastrointestinal diseases has been omitted.

SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN NEUROLOGY

Neurology as a science had its beginning in the 19th century with the recognition of neurological syndromes and diseases. Before that time, however, there had been many isolated neurological observations. Galen, the Greek physician (130–200), knew the effect of a severed spinal cord; Thomas Willis of England (1621–1675) classified the cranial nerves and gave the most complete description of the anatomy of the nervous system of his day; and Thomas Sydenham (1624–1689), also of England, published classic first-hand accounts of many diseases, among them chorea.

During the 19th century, there were many outstanding neurologists who laid the foundation for modern neurology. It would be difficult to list them all here, but the following men advanced certain theories and techniques used today in research laboratories or in the clinical treatment of neurological and sensory disorders.

James Parkinson, an English physician, described in 1813 the first recognized case of paralysis agitans, and John Hughlings Jackson (1834–1911), also English, concluded from clinical and postmortem studies of epilepsy, aphasia, and paralysis that certain cortical areas were concerned in motor activities, sensory mechanisms, and language.

Jean Cruveilhier (1791–1874) of France may be considered as one in the long ancestry of the modern science of neuropathology. He is credited with the first classical description of disseminated sclerosis in 1835.

Pierre Paul Broca (1824–1880), French, was the first by demonstration to correlate the language functions with definite areas of the brain.

World-famous Jean Martin Charcot (1825–1893), the father of modern neurology and neuropathology, created in the Salpetrière, out of a Paris bedlam of 5,000 mentally or neurologically ill persons, the greatest neurological clinic of his time. He distinguished between the tremor of Parkinson's disease and that of multiple sclerosis, and showed tremor as a symptom and not a disease in itself. Charcot, by astute clinical observations and crude methods of free-hand sectioning and staining, actually built the present clinical neuropathological basis of multiple sclerosis. From the standpoint of pathology, etiology, and classification of this disease, we have not advanced very far beyond his original work. Charcot is well known for his clinical anatomical approach to the study of the central nervous system, and he was the first to describe amyotrophic lateral sclerosis. He was a leading discoverer in anatomy and physiology of brain and nerves, and a teacher of pupils who became famous.

Vittori Marchi (1851–1908), the Italian physician, established the neuron theory by developing a method for straining degenerating fibers and applying it to experimentally produced lesions.

Sir Victor Horsley of England in 1888 described decompressive procedures for the relief of inoperable brain tumors. Of 44 operations he performed on the brain, there were only 10 deaths, most of which were malignant growths. At a time when brain operations were usually fatal, and speed was a prime factor in surgery, this was an astonishing record.

Josef Babinski of France in 1896 described the pathological reflex of the toes which occurs in central nervous system disorders. This cutaneous plantar reflex, a neurological sign known as the Sign of Babinski, has no equal in its simplicity, diagnostic importance, and physiological implications. Babinski's studies on the plantar reflex will probably stand as his greatest single contribution to medicine, but his other clinical discoveries are of equal significance.

Arthur van Gehucten, Belgian anatomist (1861–1914), found a method for rapid diagnosis of rabies based on histological changes in the nervous system. He proposed a specific surgical procedure for the treatment of trigeminal neuralgia. His exhaustive studies on the nature of motor disturbances in cerebral palsy have added to our present knowledge of this disorder.

At the beginning of the 20th century, Nobel prizes were awarded for remarkable discoveries in physiology and medicine. It is important to note here that before and since this time, there have been many equally significant discoveries opening new vistas in the neurological field which have not received such public recognition.

First in the series of Nobel prize winners in physiology and medicine was the Russian Ivan Pavlov (1849–1936), one of the most dynamic, brilliant, and zealous scientific figures of all time. He received the Nobel prize in 1904 for his work on the physiology of digestion.

The well-known Spanish neuroanatomist, Santiago Ramon y Cajal (1852–1934), shared the Nobel prize in 1906 with Camillo Golgi (1844–1926), Italian histologist, for their work on the structure of the nervous system. Cajal combined the visualizing talent of an artist with the skilled observation of a physician to produce medical drawings exceeded only by his plates for microscopic study of nerve tissue. On these tissues, he used his own improvement of Golgi's pioneering silver staining which made possible the discovery of "Golgi cells." Professor at the University of Madrid and prolific author of 74 books and 286 monographs, Ramon y Cajal provided evidence for the neuron theory of separate nerve cells by his research.

In 1911 Allvar Gullstrand (1862–1930) of Sweden was awarded the Nobel prize for his work on the dioptrics of the eye. Gullstrand gave the first explanation of the heterogenous structure of the lens on physiological grounds. His work contributed to the present knowledge of the structure and function of the eye and he devised the first reflex-free ophthalmoscope.

Archibald Vivian Hill, prominent English physiologist, was awarded the prize in 1922 for his discovery relating to the production of heat in the muscles.

Christian Eijkman (1858–1930) of Holland was awarded the 1929 prize for his discovery of the antineuritic vitamin. He called his discovery of the cause and cure of the multiple neuritis, beri-beri, "an accident." Among the half dozen pioneers in vitamin study, he was a member of a commission to the Dutch East Indies which vainly

looked for a bacterial cause for beri-beri. He observed that chickens fed polished rice developed polyneuritis and that unhulled rice prevented and sometimes cured these chickens. He extracted the effective antineuritic principle, Vitamin B_1, and used it as a remedy by mouth or injection.

Charles Scott Sherrington (1857–1952) and Edgar D. Adrian (1889–), both of England, shared the Nobel prize in 1932 for their discoveries regarding the function of neurons. Sherrington provided that nerves going to muscles carry sensory fibers for perceiving as well as motor fibers for action. His experiments on sense of position and equilibrium guided the clinical neurologists. His more exact mapping of the brain surface explained hemiplegia (paralysis of one side of the body) and the manner of recovery. Adrian built upon and extended Sherrington's researches and developed their value.

In 1936 Henry Hallet Dale, English, and Otto Loewi, German, shared the Nobel prize for their discoveries relating to the chemical transmission of nerve impulses.

PRESENT NEUROLOGICAL RESEARCH IN OTHER COUNTRIES

Australia.—Sir John Carew Eccles, of the Australian National University at Canberra, and his group are making outstanding contributions in the field of neurology through studies on physical properties of spinal motoneurones, and have initiated new experiments dealing with organization of spinal pathways.

Belgium.—Dr. Ludo van Bogaert, in association with the Institut Bunge in Berchem-Anvers, is one of the most prolific contributors to neurology and neuropathology, particularly in the fields of multiple sclerosis, other demyelinating diseases, and encephalitis.

Dr. Jules Francois, Eye Department at Gand, presents a continuous flow of valuable information from one of the most productive ophthalmological centers. His specific contributions are in clinical and morphological studies on intraocular pressure, studies on the chemistry of the lens, and on the function of the retina in health and disease.

Denmark.—In Copenhagen, Drs. B. Harvald and M. Hauge are doing research on genetic factors involved in brain tumors among relatives. In multiple sclerosis, Dr. Kay Hyllested is conducting a long-term detailed investigation of incidence and geographic distribution and Dr. Paul Thygerson is responsible for a detailed monograph on clinical and pathological aspects.

England.—At England's largest neurological hospital, the Queens' Square National Hospital, Dr. J. Cummings has contributed original research on heavy metals in Wilson's disease. More recently, he made discoveries in the study of gangliosides in reference to lipid abnormalities in the brain.

Professor Bernard Katz, London, is conducting studies on the submicroscopic structure of the neuromuscular junctions. Important findings on the relation between mitochondria and synaptic vesicles have been obtained.

From Cambridge, the Hodgkin-Huxley hypothesis of nerve message transmission governs all intracellular physiology in most advanced countries. Hodgkin has completed a quantitative study on the origin of the membrane potential of vertebrate muscle fibers (equilib-

rium potential for potassium and chloride) and is engaged in experiments on the coupling between electrical activity and contraction. Huxley has shown, by means of local stimulation, that contraction occurs because of shortening of the I bands and that the process is initiated following depolarization of the cell's membrane. More recent results show that the endoplasmic reticulum is probably responsible for transmitting excitation from the cell's surface to the depth of the fiber.

Dr. W. A. Rushton, also of Cambridge, has carried forward his studies on vision and has produced convincing new evidence on physiology and pathology of color vision.

The Institute of Ophthalmology, London, under the direction of Sir Stewart Duke-Elder, continues to publish important studies dealing with physiological problems connected with electrophysiology, pathology, and physical chemistry.

France.—Neurology training and research, established by Charcot at the Salpetrière, is being continued by Professor Th. Alajounanine and Dr. Raymond Garcin. Professor Fessard, Collège de France, and Dr. Arvanitaki at Lyon, independently study basic problems of excitation of invertebrate nerve structures, while Professor Couteaux continues his known studies on the morphology of the neuromuscular junction. Professor Henri Gastaut is continuing his original investigations on the mechanisms of conditioning. Dr. Antoine Rémond of the Paris Medical School, considered one of the leading electroencephalographers of Europe, is improving methods for the study of the total pattern of the electrical activity of the brain.

Germany.—At the University of Bonn, Professor H. K. Müller is making significant contributions to the field of chemistry of the lens, and Dr. G. Meyer-Schwickerath has developed a new treatment for retinal detachment, using a light source instead of electrical current. In Hamburg, Dr. med. Heinrich and Frau Professor Pette are conducting research on multiple sclerosis and the possible effect of virus on the central nervous system, as well as work on allergic encephalitis.

Italy.—Dr. Ernst Chain, recipient of the 1945 Nobel Prize for his work with penicillin, has completed a study of intermediary carbohydrate metabolism of brain and muscle, and Bovet pursues pharmacological experimentation with various neurotropic compounds.

In Pisa, Moruzzi has recently published a comprehensive monograph on the cerebellum, while his pupils have completed a review on the physiology of the reticular substance. Dr. di Francia and others study various aspects of visual processes mainly with the use of psycho-physical techniques.

In Milan, Margaria works on effects of acceleration upon the central nervous system. He is a regular consultant for the United States Air Force, and his important results were recently presented here in Washington. Bairati (electron microscopy) analyzes structural-chemical relationship in the central nervous system. In Padua, Cardin works on de-afferentation and spinal cord physiology.

Japan.—In Tokyo, Dr. H. Schiraki is concerned with significant projects on pathology associated with the central nervous system, the effect of atomic radiation, and allergic encephalitic myelitis in association with rabies vaccine.

Dr. S. Okinaka, Professor of Medicine at the University of Tokyo, is conducting epidemiology studies on the incidence and geographic distribution of multiple sclerosis in Japan.

Sweden.—Frankenhäuser has developed a method for studying the course of membrane conductance of nodes of Ranview during excitation (voltage-clamp method). Professor Granit continues his studies of the relations between reflex activity of large and small spinal motoneurones, while Skoglund has collected important data on several features of the activity of spinal interneurones.

The work on receptors and sensation is continued by Zotterman and his coworkers with recent communications concerning questions of taste and thirst.

Dr. Torsten Sjogren, an outstanding geneticist, is conducting investigations using as a principal source detailed pedigree reports going back over 350 years.

Considerable brain research is being carried on at the Kungliga Karolinska Institutet in Stockholm.

U. S. S. R.—Professor N. I. Grashchenkov, Director of the Neurological Clinic at Central Institute for the Advanced Training of Physicians, Ministry of Health, Moscow, has presented a documentation of the Soviet program in clinical neurology under the Sixth Five-Year Plan which should be of interest to neurologists in the United States and other countries.

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SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN THE FIELD OF MENTAL HEALTH AND MENTAL ILLNESS

PSYCHIATRY

The modern era in the care and treatment of the mentally ill did not begin until the end of the 18th century. However, some of the leading thinkers during the classical Greek period made important contributions.

Pythagoras (580–510 B. C.) and his pupil Alcmaeon (550–500 B. C.) are said to be the first Greek philosophers to identify the brain as the central organ of intellectual activity, and to regard mental disease as a disorder of that organ. Pythagoras also pioneered in experimental investigations of animals.

Hippocrates (460–370 B. C.) was the first to emphasize predisposition and heredity in relation to mental disorders, and to recognize a relationship between elation and depression, which Kraepelin more than 2,000 years later showed to be different phases of the same disorder. Neurasthenia, psychasthenia, hypochondria, obsessions, compulsions, and phobias were recognized as pathological conditions in the Hippocratic era.

Plato (427–347 B. C.) taught that the balance between the body and soul was the important element in health. He believed that mental disorders could arise from either bodily or moral disturbances, and that physical health, education, strengthening of the mental faculties, and correct living habits were prophylactic.

One of the very early references to special protection for the insane is found in Plato's *Republic*: "If anyone is insane let him not be seen openly in the city, but let the relatives of such a person watch over him at home in the best manner they know of, and if they are negligent, let them pay a fine."

In 1793, Dr. Philippe Pinel (1745–1826), physician to the Bicetre Hospital and the Salpetrière in Paris, liberated many patients who had been in chains for as long as 30 years. He accomplished this at the height of the French Revolution, in the face of much obstruction and dire threats from the Commune.

Pinel established a medical view of mental disease as opposed to the earlier theory of "demoniacal possession." Using a new drug, "kindness," Pinel encouraged the humane treatment of the insane.

Pinel's reforms came about as a part of the growth of the humanitarian movement in Western Europe. In an atmosphere in which "the inalienable rights of man" were recognized, mental disease began to be looked upon as the misfortunes of man as a person.

Pinel's "moral treatment" was carried forward by his student, Dr. Jean Etienne Esquirol (French, 1772–1840), whose principle was: "One has to love the mentally sick in order to be worthy and capable of serving them." Esquirol continued the great reforms not only in

Paris but all over France, where he founded some ten asylums. His textbook, published in 1838, is a reflection of the most advanced thinking of the time. It was one of the first to contain statistical applications to the phenomena of mental disease. He stated that in the Bicetre 409 out of 1,570 men, and in the Salpetrière 580 out of 1,940 women, became mentally ill as a result of psychological factors.

Contemporaries of Pinel in other countries made important efforts at reform. In England, William Tuke and Lindley Murray established in 1796 the York Retreat, which was to serve as the model for many early American mental hospitals. In Germany, Fricke in 1793 was the leader of a similar movement; and Reil in 1805 founded the first journal on mental illness—"Magazin fur Nervenheilkunde."

In the United States, Dr. Benjamin Rush (1745–1813), who was appointed to the Pennsylvania Hospital in 1783, urged American physicians to respond to the needs of the insane. Rush is commonly regarded as the father of American psychiatry. His textbook, *Medical Inquiries and Observations Upon Diseases of the Mind* (1812), was the American authority on mental disease until the 1880's.

But even more than the great reformer-physicians, a retired schoolteacher, Dorothea Lynde Dix, single-handedly revolutionized the care of the mentally ill. Reaching as she did the Congress of the United States, the Houses of Parliament in England, and numerous State Legislatures, she was personally responsible for the founding of Saint Elizabeths Hospital and 31 other institutions in the United States and Great Britain, as well as for sweeping changes in existing asylums.

Beginning with Pinel, scientific psychiatry began to flower in France. Esquirol, Baillarger, Ferrus, Falret, Bernheim, Charcot, and Morel led the way with careful descriptions of mental disease. They were the first phenomenologists in modern psychiatry. However, they distrusted any attempts at classification because they felt that classification should spring from sound findings, and they did not regard psychology as sound.

In England and in Germany, the influence of Thomas Willis and Rudolf Virchow was reflected in numerous studies of the morbid anatomy of the brain of patients who died during the course of mental disease. Maudsley and Skae, Griesinger and Friedreich were among the leaders of the school of extreme somatology as was Theodor Meynert, Freud's teacher.

Gradually, however, the Germans returned to Hippocratism, to the recognition that a good understanding of the course of a disease is as important as the knowledge of its cause. Karl Kahlbaum (1828–1899) was inspired with the thought of applying the principles of natural science to clinical psychiatry. He and his pupil Hecker described catatonia, cyclothymia, and hebephrenia. This trend culminated in the monumental studies of Emil Kraepelin (1856–1926), who gave us the classification of mental disease which forms the basis of the one in current use. Kraepelin was a student of the German experimental psychologist, Wundt, and utilized Wundt's approach in studying mental abnormalities experimentally and in quantitative terms. His work covered the whole field of psychiatry, although it was his prognostic phenomonological, and descriptive delineation of

dementia praecox and of manic-depressive psychosis which had the greatest impact.

Born in the same year as Kraepelin, Sigmund Freud (1856–1939) had perhaps an even greater effect on psychiatric thinking. A gifted clinical neurologist, he studied with Charcot and Bernheim and, while at the Salpetrière, became impressed with the possibilities of psychological causation of psychological processes. He broke from the traditional thinking of his teachers, and revolutionized the field of psychopathology.

Freud introduced the objective method of studying the subjective conscious and unconscious states of his patients, thus for the first time raising the psychic apparatus to the status of a subject suitable for scientific scrutiny. His contributions have ranged into normal psychology and led to a disappearance of the strict borderline between normal and abnormal psychology. He gave substance and impetus to that view of man which regards him as a totality, and which includes his highly subjective fantasies and thoughts along with his more objective behavior in its study of his adaptation and creativity.

With the outstanding achievements of Kraepelin and Freud at the turn of the 20th century, psychiatry began to move forward more rapidly. Several others made notable contributions and were slightly overshadowed only because they were contemporaries of these two giants. Forel, Eugen Bleuler, and Carl Jung in Switzerland; Kretschmer, Wilmanns, and Wernicke in Germany; Ferenczi in Hungary; von Jauregg in Vienna; Adolf Meyer, Karl Abraham, and William A. White in the United States; Janet in France; and Gjessing in Norway are but a few of those whose fundamental studies have laid the foundations upon which our present knowledge is based.

Many other outstanding European and American contributors to 20th century psychiatry could be mentioned. A number, like Franz Alexander, Karen Horney, Adolf Meyer, and Frieda Fromm-Reichman were European born and came to this country from Austria and Germany. Others like Harry Stack Sullivan, Nolan D. C. Lewis, Abraham Brill, and Trigant Burrow were American born.

Present-day leaders in Europe include—

1. Manfred Bleuler, Professor of Pyschiatry at the University of Zurich, son of the famous Eugen Bleuler. He is a leader in European research in biological psychiatry, and is particularly interested in the relations between psychological changes and endocrine dysfunction. He has studied extensively in the United States.

2. Jean Piaget, Professor of Child Psychiatry at the University of Geneva, who has made brilliant contributions to the understanding of child development.

3. Henry Ey and Paul Dell of the Hôpitaux St. Anne in Paris. Ey is the foremost clinician on the Continent, and has made detailed clinical studies of the major illnesses which remain unequalled in their sensitivity and scope. Dell is one of the world authorities on the effects of neurohumeral agents on the electrical activity of the brain. He, too, has been a frequent visitor to the United States.

4. Daniel LaGache, Director of the Psychological Institute of the University of Paris. He is both a psychiatrist and the foremost clinical psychologist in France.

5. A. H. Theorell, Director of the Nobel Medical Institute in Stockholm. Winner of the Nobel Prize in 1955 for his discoveries concern-

ing the nature of oxidative enzymes, he has recently become interested in the possibility of an enzymatic process as the cause of mental disorders.

6. Professors Ørnulf Ødegaard and Gabriel Langfeldt, University of Oslo, Norway. Ødegaard and Sjögren (in Stockholm) are outstanding authorities on hereditary aspects of mental illness. Langfeldt is one of the leading phenomenologists in the study of schizophrenia.

7. The field of social psychiatry is far more advanced in Europe than in the United States. Among the leaders in this field are Professor Arne Querido, University of Amsterdam; Dr. Paul Sivadon, Medicin-Chef, Centre de Traitement et de Readaption Sociale, Neuilly-sur-Marne; Dr. Maxwell Jones, Belmont Hospital, Surrey, Dr. Duncan Macmillan, Nottingheam; and Dr. George Bell, Melrose, Scotland.

8. Professor Aubrey Lewis, Institute of Psychiatry, Maudsley Hospital, London. He is the most influential psychiatrist in England and plays a major role in psychiatric training and research.

9. Hans Jurgen Eysenck, Professor of Psychology, Maudsley Hospital. He occupies a central position in the field of clinical psychology, and has made many important contributions to the study of personality and to the evaluation of psychotherapy.

10. Geoffrey Harris, Fitzmary Professor of Physiology, Maudsley Hospital. His major research has been concerned with the neutral control of the pituitary gland. His work represents an area of overlap between psychological and endocrine processes.

11. Oliver Zangwill, Professor of Experimental Psychology, University of Cambridge.

12. Derek Richter, Director of Neuropsychiatric Research Center, Whitechurch Hospital, Candiff. He has carried out extensive studies of intermediary metabolism in patients with mental disorders.

PSYCHOLOGY

A good share of present-day knowledge of mental phenomena has developed out of the experimental study of psychology, which, as a field, has deep historical roots in physiology.

Among some of the nineteenth century pioneers in this field were three Germans who successively taught at the University of Leipsig: *E. H. Weber*, *Gustav Fechner*, and *Wilhelm Wundt*. Weber (1795–1878), originally a professor of anatomy and physiology, applied to studies on sensation the procedures already accepted in medical research, developing the concepts of the "threshhold" and the "just noticeable differences." Fechner (1801–1889), taking up where Weber left off, developed the intricate study of psychophysics which he defined as "an exact science of the functional relation or relations between body and mind." Wundt (1832–1920) was the founder, at Leipsig, of the first laboratory for experimental psychology, a laboratory independent of the laboratory for physiology. Wundt dominated late 19th century psychology, "permanently impressing his empirical spirit upon it," and giving a unity to psychology as a field which no one else of his time conceived.

William James (United States, 1842–1910), a brilliant New England philosopher and psychologist, was influenced by the work of

Charcot and Janet in French psychiatry. Among his many psychological interpretations, James sought to show that emotions have no existence whatever apart from physiological changes.

Alfred Binet (1857–1911), a Director of the Laboratory of Physiological Psychology at the Sorbonne, is best known for the development of the Binet-Simon scale, which marked the real beginning of intelligence testing as we know it today.

Herman Ebbinghaus (1850–1909), the German experimental psychologist known for his pioneering experiments on memory, was much influenced by Fechner. Ebbinghaus' work marks the first real attempts to apply precise scientific method to the study of higher mental processes. He showed conclusively that the products of memory are as capable of measurement as any natural fact with which science deals.

The twentieth century saw the development of three psychological schools—born as protests, taking widely varied forms, against the whole traditional conception of psychology as the analysis of conscious states. These three schools were Behaviorism, Gestalt psychology, and psychoanalysis.

1. "*Behaviorists*" followed a psychology of action rather than thought, a psychology of physiological processes based upon the physics and chemistry of the response of living tissue. Among the behavioral psychologists were Jacques Loeb (German, immigrated to United States); Nobel prize winner I. V. Pavlov, famed Russian of the "conditioned reflex" experiment; J. B. Watson (United States, 1878–1958), student of infant conditioning and learning; and Edward L. Thorndike (1874–), student of animal psychology whose work marks the real beginning of the modern laboratory approach to problems of learning and habit formation.

2. Max Wertheimer (German), the founder of *Gestalt Psychology*, and his principal followers, Koffa and Kohler, hold that complex human and animal behavior cannot be explained as an aggregation of stimulus-response bonds. They emphasize organized wholes, or Gestalten, as the real data of experience and direct their study to these configurations.

New understandings in social psychology came through the contribution of Kurt Lewin, a former member of the Gestalt group at Berlin, who immigrated to the United States. Lewin's "field theory" concepts profoundly influenced the development of American social psychology.

3. Psychoanalytic contributions (mentioned above under psychiatric advances) also had a major influence on the development of 20th century psychology, both clinical and experimental.

Among some of the outstanding present-day European contributors in psychology are Jean Piaget (Swiss) who has contributed to knowledge of judgment and thought processes in children, Muzafer Sherif (Turkish-United States), social psychologist; Herman Rorschach, the Swiss psychiatrist who devised the Rorschach "ink-blot" test as a diagnostic tool now widely used by psychologists; and the ethologist Konrad Lorenz (German) and N. Tinbergen (Dutch), who have demonstrated the critical importance of very early experience in animal and bird life ("imprinting"), which has resulted in reexamination of the concept of "instinctive" behavior.

PSYCHOPHARMACOLOGY

A very early reference to the treatment of the mentally ill through drug therapy occurs in the correspondence of Democritus (470–460 B. C.–420 B. C.) with Hippocrates. Democritus notes that he had observed the different effects of a drug in different situations, a phenomenon that has served as a focus for research on pharmacology and in medical clinics for many years. Wrote Democritus: "Hellebore when given to the sane pours darkness over the mind, but to the insane it is very profitable."

Foreign Scientists Working in Psychopharmacology

Rustom Jal Vakil (*Indian*), in 1949, published a paper on the hypotensive effects of *Rauwolfia serpentina* which stimulated interest in the drug among European and American workers.

P. Charpentier, at the laboratories of Rhone-Poulenc-Specia (France), synthesized the drug chlorpromazine in December 1950 as part of a long-term project to synthesize derivatives of phenothiazines as antihistamines.

P. Deniker (*France*) was one of the pioneers in the use of chlorpromazine in psychiatric practice.

H. Laborit (*French*) used chlorpromazine in the "lytic cocktail" to produce hypothermia and artificial hibernation for surgery. He noticed that it had a tranquilizing effect on agitation and anxiety.

P. Broussolle (*French*) was one of the pioneers in the clinical use of chlorpromazine. In 1953 he published a paper on the use of chlorpromazine in treating psychotics.

Erik Jacobsen (*Denmark*) has been working at both the clinical and animal experimental level with drugs that are used in mental illness.

Albert Hoffman, a Swiss chemist, discovered the psychological effects of lysergic acid diethylamide (LSD, a psychotomimetic agent) in 1947 when he was working with the drug and noticed that he experienced vertigo and "blurring" of mental alacrity.

Heinrich Kluver (*originally German but now a United States citizen*) has done valuable experimental work with mescaline.

Heinz E. Lehmann (*originally German, now Canadian*) has done extensive clinical work with psychopharmacological agents, particularly chlorpromazine, and has demonstrated the practical uses of these drugs.

Joel Elkes (*originally English, recently immigrated to the United States*), has done, and continues to do, valuable clinical and experimental work in psychopharmacology. He is now Chief of the NIMH's Clinical Neuropharmacology Research Center, located at St. Elizabeths Hospital in Washington, D. C.

J. M. Miller, E. Schlitter (*now in the United States*), *and H. J. Bein* synthesized reserpine, an alkaloid of *Rauwolfia serpentina* (published in 1952 in *Experientia*), and showed that it had a prolonged hypotensive action and quieting influence in animals.

U. S. Scientists in Psychopharmacology

Nathan S. Kline (*United States*) was the first American to demonstrate the value of reserpine in treating mental patients.

Robert H. Noce (*United States*) has contributed in demonstrating the use of reserpine in the mentally ill and in mental defectives.

James Olds (*United States*) has made a major methodological contribution in developing a technique for direct self-stimulation of the brain with drugs, used in neurophysiological research on animals.

Harold E. Himwich (*United States*) has contributed to the understanding of the physiological and pharmacological effects of psychopharmacological agents and of their modes of action.

Neal Miller (*United States*) is a major contributor to this field in the area of experimental psychology.

In 1957 Rustom Jal Vakil, Nathan S. Kline, Robert H. Noce, Henri Laborit, Pierre Deniker, and Heinz E. Lehmann received Lasker awards for their contributions in this field.

NEUROLOGICAL RESEARCH

British, European, and American neurophysiologists have traditionally been more concerned with neurons and neuronal systems than with the psychological problems involved in the activity of the brain. This tradition stems from the time of René Descartes, in the first half of the 17th century, who gave convincing arguments for locating all psychological properties in the pineal gland.

During the mid-19th century, a group of physiologists, led by men like Johannes Müller, du Bois Reymond, Carl Ludwig, and Hermann von Helmholtz, sought to give physiology a basis in chemistry and physics. They, and such contemporaries of theirs in France as Francois Magendie and Claude Bernard, helped shape the tradition which physiology follows today and which is reflected in the work of such men as Sherrington.

By contrast, such Russian physiologists as Sechenov have attempted to develop generalizations which would account for psychological and physiological properties of the nervous system at the same time. More recently, attempts have been made to reconcile the two traditions by such outstanding physiologists as Jerzy Konorski of the Nencki Institute of Experimental Biology in Poland.

In this field mention must be made of J. L. W. Thudicum, the 19th-century scientist who is commonly regarded as the father of neurochemistry and who made outstanding contributions to the field of physiological chemistry.

Following is a list of some of the more important researchers in neurology throughout the world today, and a brief description of their specialized fields of work:

France

Paris. Professor A. M. Monnier and his colleagues at the Sorbonne have been conducting studies on biochemical and bioelectrical mechanisms relating to the nerve membrane.

Alfred Fessard, Professor at the Collège de France, Directeur de l'Institut Marey, together with about a dozen coworkers, is investigating a wide range of general neurophysiological problems, including the origin of brain waves (EEG); central nervous mechanisms concerned in arousal and the focus of attention; and the neuromuscular junction and electric organ in the eel and torpedo fish.

Paul Dell, Laboratory of Physiology, Hôpital Henri Rouselle, is studying the influence of biochemical agents and natural biologics, such as hormones, on brainstem mechanisms concerned with arousal and emotional reaction.

Lyon. Dr. Michel Jouvet, in the Faculté de Médecine of the University of Lyon, is studying the central nervous mechanisms involved in conditioned learning.

Marseille. Jacques Paillard, Laboratoire de Psychophysiologie de la Faculté des Sciences de Marseille, is studying clinical neurophysiology, particularly as it relates to the mechanisms of central motor command.

Professor Henri Gastaut and a group of coworkers are studying the electrophysiology of classical Pavlovian conditioning.

Toulouse. Dr. Yves Laporte is doing basic work on synaptic conduction.

Belgium

Brussels. Professor Frederick Bremer leads a prominent school of neurophysiologists studying mechanisms relating to sensory arousal, origin of brain waves (EEG), mechanisms of graded response, and brain circuitry in general, including important work on the cerebellum.

Pierre Rijlant has probably the best instrumented physiological center in Europe. This enables him to study multichannel recording systems involving, in some cases, nearly 200 channels recorded simultaneously. He uses these to analyze the spontaneous activity in the brainstem centers connected with respiration and blood pressure control. He also has studied the pattern of excitation of the cardiac musculature during normal states and during abnormal conditions, such as fibrillation.

Denmark

Copenhagen. Dr. Fritz Buchthal and his wife (Dr. Margaret Lennox) are doing important studies on the biochemistry and biophysics of muscle and nerve-muscle mechanisms and on the central nervous system correlates of color vision.

Sweden

Stockholm. Professor Ragnar Granit at the Nobel Institute is one of the most outstanding neurophysiologists of our day. He has done pioneering work on mechanisms of the retina and of a number of central pathways relating to sensation. He has been prominent in studies concerning central mechanisms governing controlled movement and posture, including studies on the muscle spindle, motor and sensory control systems, and their relationship to segmental reflexes and particularly to brainstem and cerebellar control mechanisms.

Professor Carl Gustav Bernhard and associates, including particularly Dr. C. R. Skoglund, are doing outstanding work on nervous mechanisms governing motor performance. Bernhard and Skoglund are in the Department of Physiology in the Karolinska Institutet.

Professor Ingve Zotterman, who is Head of the Department of Physiology in the Veterinary School, has done pioneeering work on the sensory mechanisms, particularly those relating to pain and to visceral sensory patterns, such as those originating from the carotid sinus and carotid body. Professor Zotterman's studies on taste and warmth receptors are also outstanding.

Professor Hugo Theorell, Nobel Medical Institute, is perhaps the most outstanding student of the physical, chemical, and biophysical mechanisms involved in the nerve membrane.

Other prominent Swedish neurophysiologists include: Ulf von Euler, who has done outstanding work on peripheral and central mechanisms relating to epinephrine, norepinephrine, and acetylcholine; Curt von Euler, Karolinska Institutet, who has studied hypothalamic and other brainstem regions relating to temperature regulation, appetite, and motor mechanisms; B. Andersson, working with Zotterman, who has done pioneering work in relation to hypothalamic drive mechanisms by direct stimulation; and Bo E. Gernandt, Professor of Physiology in Gothenburg, who is the world's foremost authority on the neurophysiology of vestibular mechanisms.

A notable Swedish neuroanatomist, Nils-Åke Hillarp, Professor of Histology at Lund, has done exceedingly fine and important work on the innervation of glands by the autonomic nervous system. Professor Holger Hydén, Professor of Histology at Gothenberg, and Dr. T. Caspersson of Stockholm are outstanding authorities in the field of applying physical methods to the analysis of the structure of cells.

Norway

At the University of Oslo are three outstanding scientists devoted to the central nervous system. Alf Brodall has investigated the anatomical connections between the cortex and the brainstem reticular formation. Professor Jan Jansen has made a brilliant analysis of the comparative anatomy of the cerebellum. Dr. Birger Kaada has studied the function of phylogenetically older parts of the brain in relation to emotion and other aspects of behavior.

Germany

Göttingen. Dr. Ulrich F. Franck in the University of Göttingen is one of the world's authorities on the physical and biophysical aspects of nerve membrane. He has succeeded in making very detailed studies of the analogies between oscillating biological systems and certain physical-chemical models.

Schwarzwald. Oskar and Cecile Vogt, although both in their eighties, are still pursuing brain research. They have concentrated largely on the cellular architecture of the cortex, especially as to the differentiation of various cortical areas.

Freiburg. Professor Richard Jung heads a small school of excellent neurophysiologists exploring mechanisms relating to brain waves (EEG), brainstem reticular formation, and arousal.

Switzerland

Zurich. Professor Walter Rudolph Hess received the Nobel Prize in 1949 for his physiological work which includes studies on blood coagulation, eye movements and, most particularly, central nervous system mechanisms involved in behavior. He has studied primarily the upper end of the brainstem including the hypothalamus. After Professor Hess retired from the University of Zurich, he was succeeded by Professor Oscar A. M. Wyss, who has done notable work on the afferent and central nervous mechanisms controlling respiration.

Bern. An important school of neurophysiology is headed by Professor Alexander von Muralt. This group has concentrated on biophysical analysis of peripheral nerves, with particular attention to mechanisms interfering with key neurochemical processes.

Geneva. Professor Jean Posternak also studies peripheral nerve, specializing in the thermodynamic aspects of the action of local and general anesthetics. More recently, he has been applying these same methods on circuits within the central nervous system.

Hungary

Pecs. Professor John Szentagothai, although a Professor of Anatomy, has conducted many important neurophysiological investigations relating to vestibular influences on posture and locomotion and the central nervous mechanisms relating to eye movements.

Poland

Warsaw. Professor Jerzy Konorski, Head of the Neurophysiology Department of the Nencki Institute, represents an important and vital bridge between classical Pavlovian neurophysiology and that represented by the English school of Sherrington.

Japan

Genichi Kato undertook to make refinements on Western neurophysiology by improved dissection techniques, including dissection of single nerve fibers. Ichiji Tasaki, his most brilliant student, is now working in the United States.

Other prominent neurological physiologists in Japan include Shimamoto, Katsuki, Hayashi, Bunichi, Fujimori, and Hajiwara.

Australia

Melbourne. Sidney Sunderland, an outstanding anatomist, has traced the mixing of nerve fibers in major nerve trunks and has done important work on the regeneration of nerve fibers.

Canberra. Sir John Eccles, a student of Sherrington, is world famous as a microelectrode neurophysiologist.

Adelaide. David I. B. Kerr was one of the first to demonstrate central nervous control of sensory nervous transmission systems.

Sidney. Peter Bishop has done excellent work on the visual pathway, including single-cell recordings in the lateral geniculate body.

India

All-India Institute, New Delhi. Bal Anand, Professor of Physiology, has analyzed hypothalamic mechanisms relating to appetite and satiety.

Dr. Liza Chacko, Professor of Anatomy, has done brilliant anatomical work, including combined anatomical and physiological studies on the visual pathway.

Great Britain

Cambridge. Lord E. D. Adrian, Master at Trinity College and Professor of Physiology at Cambridge, probably the most distinguished of all physiologists, has done pioneering work in every aspect of sensory mechanisms.

Sir Brian Matthews has done distinguished work on sensory mechanisms relating to muscle and other proprioceptive systems. He is a pioneer in work on single-unit activity in the peripheral nervous system.

Alan Hodgkins heads a group of notable neurophysiologists concerned with fundamental membrane mechanisms related to the role of ion fluxes in neuron activity. His group includes Andrew Hux-

ley, Richard Keynes, and Richard Adrian, an outstanding team of scholars.

London. J. Z. Young, Professor of Anatomy at the University of London, has done experimental work on learning and memory in connection with specific parts of the nervous system of the octopus. Also at the University of London, Dr. Donald Sholl has done important work on the microarchitecture of the cerebral cortex.

Geoffrey Harris at Maudsley Hospital is working on hypothalamic endocrine relationships. A. E. Carmichael at Queens Square is studying autonomic mechanisms in relation to physiology and psychology.

Oxford. Le Gros Clark, Professor of Anatomy, has done broad work in the fields of anthropology and neuroanatomy. Other outstanding scientists in this department include Paul Glees, the neuroanatomist, and Graham Weddell, who has done important work in tracing fine nerve fibers.

Bristol. Grey Walter has done pioneering work on the EEG.

Edinburgh. David Whitteridge is working on the nervous mechanisms related to the control of eye movements and sensory receptors.

SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN DENTISTRY

We know that disease is as old as life itself, that dental disease is as old as man, and that necessity which inevitably gives birth to invention, must have early taught man to use some means for cure or alleviation of pain. The prehistoric man who knocked out his aching dentition with a stone chisel started the practice of exodontia, and the medicine man who conjured the evil spirit to depart from a swollen jaw was practicing dental therapeutics.

For a long time, there was almost no progress, and it was not until 4000 B. C. that drugs and other remedies started to compete with magic and witchcraft for the relief of dental disorders. The Romans combined Greek medical knowledge with Etruscan mechanical skill and developed the practice of dentistry to a surprisingly high level for that time. After the fall of the Roman Empire, there was virtually no progress recorded in the dental arts or science until the 14th century, when the gross anatomical observations of *Guy de Chauliac of France* and *Bartolomaeus Eustachius of Italy*, two noted anatomists, led the way toward new gains which were to find practical application in the work of *Pierre Fauchard* at the end of the 17th century.

Eustachius (*1520–1574*) gave us a complete anatomical description of the teeth and their development in every age of growth from early uterine life until the eruption of the third molar. He also discovered the periodontal membrane, which he correctly described as "very strong ligaments principally attached to the roots by which these latter are tightly connected to the alveoli." *Eustachius* is of special interest because he wrote the first book ever published devoted entirely to dental anatomy. A small volume of only ninety-five pages, it covered accurately the anatomy, embryology, and physiology of the teeth, including the blood and nerve supply.

Fauchard (*1678–1761*) was one of the most widely respected and commanding figures in dentistry and has been referred to as the founder of modern dentistry. He was the first of a group of renowned dental scientists of France. Among these were such men as *Geraudly*, *Bunon*, *Hurlock*, *Mouton*, *Tolver*, *Lecluse*, *Pfaff*, *Bourdet*, *Jourdain*, *Serre*, and *Ruspini*. *Fauchard* was one of the first of the dental profession to become interested in the importance of the diseases of the teeth and mouth in relation to bodily health.

Famous among the names in the 17th century was that of *Leeuwenhoek* (*1632–1723*), maker of the most powerful microscopes then available. He discovered the dental tubuli, which he described as being so fine "that six or seven hundred of them are no thicker than the hair from one's head." *Leeuwenhoek* also examined material scraped from tooth surfaces and was the first to see the microorganisms which inhabit the human mouth.

Malpighi (1628–1694), the noted Italian anatomist, made use of the microscope for observation on tissues including those of the gums, and is regarded as the founder of histology.

In England in *1685*, *Charles Allen* published the first dental works in the English language, writing of his success in transplanting human teeth. In *1771 John Hunter* published his now famous book, "The Natural History of the Human Teeth," which laid the foundation for scientific dentistry in the English-speaking world. In *1803 Joseph Fox*, a practicing dentist, authored a significant book entitled, "The History and Treatment of the Disease of Human Teeth," which amplified the works of his former teacher, Hunter, and wielded considerable influence on the dental profession both in England and in Colonial America. These early researchers on the continent and in the British Isles were often dentists recording their observations, and they helped to build their branch of the healing art into a scientific profession.

Artificial teeth of baked porcelain originated in France in 1774, and for several decades Paris remained preeminent as the capital of dental art. On the scientific side, however, it was the meticulous research works of the English that eventually exerted the more powerful influence.

Since about the middle of the 19th century, most of the progressive dental technics and appliances have originated in the United States. The foundations were laid by Hayden and Harris when they organized the first separate school for the training of dentists in Baltimore in 1840. During the last decades, the developments in the art and science of dentistry in the United States have been phenomenal, largely due to the schools, the societies, and the numerous professional publications. Early in this same century, however, Europe and Scandinavia came to the forefront again. The X-ray was a German invention; cocaine was developed by an Austrian; and credit for directing attention to focal infection belongs to a British physician, *William Hunter (1718–1783)*, who contended that while chronic tooth abcess may do little damage at the point of its original location, infectious organisms might enter the blood stream and lodge in some vital organ or tissue, thereby becoming a menace to health, or to life itself.

Although America became the most fertile site of developments in dentistry in the latter part of the 19th century and 20th century, many of these developments can be indirectly attributed to fundamental contributions made in other centuries. During this period, there were many milestones and events worthy of mention. Some of these include: *Dr. Crawford W. Long's* discovery of ether anesthetic in 1842, followed in 1844 by *Dr. Horace Wells'* perfection of the use of nitrous oxide as a dental anesthesia; development of the dental foot-engine by *Morrison* in 1872; *Köller's* suggested use of cocaine hydrochlorate for topical anesthesia; *Angle's* system of orthodontia in 1887; development of balanced amalgam alloys and scientific cavity preparation promulgated by *G. V. Black* in 1891; *Roentgen's* discovery of the X-ray in 1895; four-year course in dental colleges established in 1903; discovery of fluoride-caries beneficial relationships in late 1930's; and establishment of a National Institute devoted exclusively to dental research in 1948.

Dentistry today is viewed more and more with the concept of man as a single biological entity and not merely a conglomeration of

parts—a concept first recognized by *Fauchard* over 250 years ago. Investigators in this country a d abroad working in both the dental and basic sciences are mounting a broadened attack in search for knowledge of the etiology of dental diseases.

Following is a current list of centers of productive dental research in foreign countries today including the names of prominent investigators and their field of interest:

Sweden

Gosta Gustafson, Lund: experimental and clinical caries.

Bengt E. Gustaffson, Malmo: germ-free research and previous significant contribution to dental caries in the Vipeholm Study.

S. T. Ericson, Stockholm: saliva chemistry—milk borne fluoride.

Denmark

P. O. Pedersen, Copenhagen: fluorides—dental caries.

England

Geoffrey Slack, Liverpool: oral flora—experimental caries.

R. L. Hartels, Liverpool: experimental dental caries.

M. V. Stack, University of Bristol: tooth chemistry—protein.

A. I. Darling, University of Bristol: mineralization in enamel.

Italy

A. Candeli, University Perugia: fluoride.

South Africa

J. T. Irving, University of Witwaterssand, Johannesburg: tooth chemistry, histology.

T. Ockerse, Praetoria South Africa: epidemiology of caries, fluoride, periodontology.

India

V. N. Potwardhan, Indian Council of Medical Research, New Delhi: nutrition.

Israel

I. Gdalia, Hebrew University, Jerusalem: fluoride.

Canada

T. T. Rac, University of Toronto: biochemistry of saliva.

L. F. Belanger, University of Ottawa: calcification—dental tissues.

C. P. Lebland, McGill University, Montreal: calcification, organic matrix.

Holland

Bracker, D. O., Laboratory of Hygiene, Utrecht: dental caries.

Germany

H. D. Cremer, University of Maniz, Maniz: fluorides, calcification.

Switzerland

H. R. Muhlemann, University of Zurich: enamel chemistry—dental caries—periodontal disease.

A. J. Held, Geneva: diet, fluoride, dental caries.

Australia

N. E. Goldsworthy, Institute of Dental Research, Sydney: dental caries control.

Norway

Nicolai Eeg-Larson, Norwegian State Dental School, Oslo: biochemistry of organic portion of bone.

Stig Schultz-Haudt, Norwegian State Dental School, Oslo: biochemistry of oral soft tissues and action of oral bacteria on them.

G. Toverud, Oslo: epidemiology—diet—dental caries.

Hungary

P. Adler, University Medical School, Debregan: caries control.

SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN THE FIELD OF BIOLOGICS CONTROL

Less than a hundred years ago, little was known of the cause or transmission of infectious diseases. Cholera, which had ravaged Asia for centuries, spread in severe epidemics throughout Europe and North America between 1830 and 1900. The plague occurred in pandemics throughout the world from the sixth century until 1840. Typhoid raged in times of famine and war, even through World War I. Smallpox disfigured countless victims, and yellow fever was one of the most devastating diseases of the 19th century.

When it was finally recognized that most of the diseases with which man was familiar were caused by living organisms so small as to be invisible to the unaided eye, it then became possible to develop the means of destroying these organisms by antisepsis; for interrupting their growth and transmission by sanitation; and for internal defense against them through immunization.

Today, in those areas of the world where it has been possible to apply this knowledge intensively, cholera, plague, smallpox, and yellow fever are terrors of the past. In other areas of the world, these diseases and others still take their toll, and constitute a safety hazard for the rest of mankind.

Twenty years ago at a conference in New York City, representatives of 61 governments agreed that low health standards anywhere in the world are a common danger and that health is consequently of world concern. The present-day speed and simplicity of international travel accentuates this danger. This was sharply emphasized by the rapid spread of Asian influenza in 1957 to many parts of the world.

Man now has at his command the basic knowledge with which to eliminate many infectious diseases from the world, but this knowledge can only be effectively applied through the cooperation of all nations.

CHOLERA CONTROL

Cholera, which for centuries had been endemic in India, invaded Europe in 1831, and since then a series of great epidemics has carried it throughout most of the world. The fourth great pandemic (1864-75) affected Asia, Africa, Europe, and America.

The agent, the cholera vibrio, was discovered in 1883 by Koch. A number of species are now known, but of these, probably only two are pathogenic—that discovered by Koch, which is pathogenic to man, and one discovered by Metchnikoff which is pathogenic to pigeons and guinea pigs.

Cholera can be controlled by proper sanitation, but in low-lying, densely populated areas, such as the delta of the Ganges River in India, sanitary facilities are limited; hence this area remains the great endemic focus of the disease. There is also evidence that the valley of

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the Yuan River in China is an endemic area. The disease spreads out from these foci each year throughout India and along the China coast.

Active immunization with vaccines has been carried out for many years. The first vaccine was that of Haffkine (1893), who used a living attenuated culture in Spain. A heat-killed vaccine discovered by Kolle (1896) was successfully used in Japan (1904). Vaccines containing cholera vibrios treated with antiserum have also been investigated. The vaccine presently used is a saline suspension of two varieties of cholera vibrios.

Although it is not known precisely how effective active immunization is, an extensive field study carried out in Madras, India (1941–42), indicated a definite protective effect of inoculation, with those immunized being 2 to 14 times less likely to get the disease.

Cooperative international investigations are presently being initiated by the World Health Organization to develop a laboratory assay of the cholera vaccine in connection with a field trial to determine more precisely its effectiveness in man.

International authorities actively working on cholera control and cholera vaccine are Dr. M. L. Ahuja, now Medical Advisor to the Ministry of Health for Indian Affairs, India House, London; Dr. D. C. Lahiri, School of Tropical Medicine, Calcutta, India; Dr. J. Gallut, Pasteur Institut, Paris, France; Dr. W. Burrows, University of Chicago (experimental cholera studies); Dr. Sahib Singh Sokhey, Haffkine Institute, Bombay, India (assay procedures); and Dr. R. Pollitzer, George Williams Hooper Foundation, University of California, San Francisco.

YELLOW FEVER CONTROL

Yellow fever was first recognized as a disease entity in the 17th century. As early as 1848, it was theorized that insects carried the infection from person to person, and in 1881 the Cuban physician Juan Carlos Finlay was convinced that the carrier was the mosquito *Aedes aegypti.* This was later confirmed by Walter Reed and his colleagues, whose work in Cuba in the early 1900's led to antimosquito measures which, by 1927, had apparently eradicated yellow fever from the Western Hemisphere.

But in 1932 the jungle form of yellow fever was discovered in Brazil, and it became clear that this disease could not be fought simply by destroying the vector. Active immunization of man was necessary. From 1932 to 1937, several types of virus vaccine were used with varying results. An attenuated, live virus vaccine was successfully used to immunize more than a million American soldiers in World War II, and won for its developer, Dr. Max Theiler, the Nobel Prize in medicine (1951).

In Africa more than 56 million persons were vaccinated between 1939 and 1953 with the "scratch vaccine" made from virus attenuated by many passages thru the brains of mice and prepared by the Pasteur Institute at Dakar. The vaccine most widely used in the rest of the world is known as the "17D strain." It contains modified virus which has been maintained in egg passage through many generations. A frozen and dried emulsion of chick embryos which is rehydrated before use, it induces an effective immunity when given subcutaneously.

Vaccination against yellow fever is officially sanctioned as a preventive method by international health legislation, which allows travelers holding a valid certificate of vaccination to avoid quarantine isolation when passing from an infected area to one receptive to yellow fever. Further, the vaccine used must be prepared in a WHO-approved laboratory.

Specialists whose names are linked with the success of the worldwide control of yellow fever are Dr. H. A. Penna, Director, Yellow Fever Laboratory, Oswaldo Cruz Institute, Rio de Janeiro, Brazil; Drs. F. L. Soper and J. A. Kerr, Pan American Sanitary Bureau, Washington, D. C.; Dr. F. N. Macnamara, Director, West African Council for Medical Research, Nigeria; Dr. J. W. Wolff, Institute of Tropical Hygiene, Amsterdam; Dr. R. Panthier, Pasteur Institute, Paris; Dr. Kenneth C. Smithburn, Rockefeller Foundation, New York; Dr. R. I. Diaz, Medical Chief, Division of Yellow Fever and Plague, Ministry of Sanitation, Caracas, Venezuela; Dr. A. Gast-Galvis, Director, Carlos Finlay Institute, Bogota, Colombia; Dr. J. Laigret, Professor of Hygiene, University of Strasburg, France; Dr. C. Durieux, former director, Pasteur Institute, Dakar; and Dr. G. W. A. Dick, Department of Microbiology, University of Belfast, Ireland.

In September 1958, at the request of the World Health Organization, a group of cholera and yellow fever experts met in Geneva to draw up international recommendations for requirements of these vaccines in order to ensure their universal safety, purity, and potency.

RABIES CONTROL

Seventy-three years ago Pasteur perfected his method for the prevention of rabies in human beings after exposure. The treatment for rabies today is basically the same "Pasteur treatment." The changes that have been introduced in the vaccine were predicted by Pasteur in 1887, when he said that an invaluable advance in the method of rabies prophylaxis would be immunization with nonvirulent material. Vaccines containing inactivated viruses, the virulence of which has been highly attenuated, are used today for treatment of human beings after exposure to rabies and for the prophylaxis of rabies in animals.

In 1940 the American workers Webster and Habel devised a method for evaluating the potency of rabies vaccine. Results of experimental and field trials in 1954, under the auspices of the World Health Organization, indicated the advantage of antiserum plus vaccine as the best prophylaxis of rabies in man in cases of severe exposure. At present, in addition to the inactivated rabbit-brain vaccine, vaccine produced from rabies-infected duck embroyos is licensed for use in man in the United States.

In 1956 an international standard for antirabies serum was established by the World Health Organization's Expert Committee on Biological Standardization. The international unit was equated with the pre-existing unit of the National Institutes of Health, U. S. A. A collaborative investigation of rabies vaccine provided by NIH is presently being carried out by WHO to determine its suitability as an international standard.

SMALLPOX CONTROL

Smallpox, or variola, is a disease of great antiquity. It was recognized in China before the Christian era, and during the Middle Ages it was prevalent throughout Europe, reaching England and spreading to America in the 16th century.

The relation between smallpox and cowpox, a disease of cattle, was clearly established in 1796 by William Jenner, an English physician, who observed that infection of human beings with cowpox protected against subsequent infection with smallpox. Today, vaccine for human use is prepared by inoculating vaccinia virus into scratches on the abdomens of calves. The "seed virus" is kept active by frequent passage through rabbits. The blisters that appear along the scratches contain the vaccine lymph, which is harvested, emulsified, tested for pathogens and potency, and stored at refrigerator temperatures for future use.

Recently, there has been much interest in the preparation of smallpox vaccine in the dried form, since this product is more stable than the presently used liquid form, which must be continuously refrigerated. In certain areas of the world, it has been difficult or impossible to stamp out smallpox because of lack of refrigeration facilities for the vaccine. For similar reasons, dried smallpox vaccine is of particular interest for military use.

So contagious is smallpox that it can spread by infected articles or dust. Vaccination is the only safeguard, and lasting protection can be assured only by regular revaccination.

Today, smallpox persists in many areas of Africa, Asia, and South America. In other areas of the world, it is practically extinct, but it is in such areas that outbreaks are more likely to occur, for these countries are probably less protected by vaccination today than at any time in the past hundred years. In the days of slow travel, there was little chance of smallpox being introduced into countries with adequate control measures. Today the disease can travel with the speed of the fastest plane. One precaution to prevent the spread of smallpox is to require that all travelers from infected areas be vaccinated and carry with them a vaccination certificate. In 1957, 120,000 cases of smallpox were reported to the World Health Organization. About 70 percent of these cases were in Asia. But as long as it persists anywhere in the world, health authorities everywhere must remain alert.

WHOOPING COUGH CONTROL

Pertussis, or whooping cough, ranked for many years among the most fatal communicable diseases of childhood.

In 1906 Drs. J. Bordet and O. Gengou, of the Institut Pasteur of Brussels, succeeded in cultivating the causative bacterium of whooping cough on a special cultural medium. The late Dr. Theodore Madsen, Director, Statens Seruminstitut, Copenhagen, Denmark, was the first to use the vaccine.

The vaccine was in and out of favor until, in 1931, Drs. P. H. Leslie and A. D. Gardner, of Great Britain, showed that the antigenic pattern of these bacteria changed on artificial cultivation and that only freshly isolated strains were suitable for preparation of prophylactic vaccines. Subsequent field trials in the United States by American workers

showed that this vaccine was effective in protecting children against whooping cough.

During this time, however, there was no suitable laboratory test to evaluate the potency of the vaccine. In 1943 American workers observed that mice could be infected when injected intracerebrally with whooping cough bacterium, and that they could also be protected by previous injection of the vaccine. This observation opened the door to the development of a laboratory potency test by American workers Dr. Margaret Pittman, National Institutes of Health, and Dr. Pearl Kendrick, Michigan State Laboratories, and others.

Following the establishment of a standard of potency for pertussis vaccine, there was a sharp tenfold drop within a ten-year period in both mortality and morbidity rates for whooping cough in the United States. The relation between the assigned standard of potency and the protection of the child, however, still remained to be determined. In the field trials (1946–56) conducted by the British Medical Research Council, laboratory-evaluated potency was shown to be directly correlated with the percentage of children protected after home exposure.

The establishment of an international unit for pertussis vaccine equivalent to that of the United States standard, which is based on extensive work done at NIH, was recommended in 1956 by the World Health Organization.

INFLUENZA CONTROL

Since 1889 influenza has been a significant cause of death in the temperate zones. The most lethal influenza pandemic—that of 1918–1919—which took a toll of 15 to 20 million victims—caught the afflicted countries almost completely unprepared. Since the casual agent was unknown, vaccination was impossible.

The discovery in 1933 of a virus responsible for influenza led to the preparation of effective vaccines which have been manufactured in one form or another for the past 12 years. Since the antigenic structure of influenza is such that a single vaccine cannot provide antigenic coverage, composition of the vaccine is subject to change. In the current influenza vaccine, there are four types of virus, including the one most recently discovered—the Asian strain.

During an influenza outbreak, the essential knowledge required is early information concerning the nature of the virus, including its antigenic structure. In order to accomplish this, the United States Armed Forces Commission on Influenza in 1941 set up a network of laboratories for the isolation of the virus, with a central reference laboratory known as the Strain Study Center.

In 1947 the World Health Organization created a World Influenza Centre and organized a world-wide network of laboratories to serve as "listening posts." Their functions are to report with all possible speed the occurrence of influenza within a country, giving an estimate of its extent and severity; and to identify the type of influenza by serological tests, and preferably by virus isolation. The virus isolated is sent immediately to the appropriate reference laboratory for further study and comparison with strains isolated elsewhere. In the case of an unusual strain, such as the recent Asian strain, it is sent to various countries for use in the manufacture of the vaccine.

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POLIOMYELITIS CONTROL

"The transformation of the relatively uncommon 'infantile paralysis' of the 19th century into 'epidemic poliomyelitis' of almost worldwide distribution presents today one of the most formidable public health problems." These words from the 1953 report of the World Health Organization's Expert Committee on Poliomyelitis summed up the gravity of the situation.

Since that time many important advances in the knowledge of poliomyelitis have been achieved. The discovery by Dr. John Enders and his colleagues (Nobel Prize winner, 1954) that poliomyelitis virus would multiply in tissue cultures of non-neural human cells led directly to the development of a poliomyelitis vaccine by Dr. Jonas Salk and his associates.

In 1954 a large-scale field trial of the Salk vaccine was undertaken in the United States under carefully controlled conditions, and in April 1955 it was announced that the vaccine was safe and effective. By late fall of that year, despite some initial difficulties, the vaccine was successfully used on a large scale in the United States, Canada, and Denmark, and on a smaller scale in Germany and South Africa.

The experience gained in these countries obviously could be of use in other countries. To facilitate an international exchange of views on poliomyelitis control, the World Health Organization's Expert Committee on Poliomyelitis was convened in July, 1957.

In June, 1958, experts responsible for biologics control in ten countries met at the invitation of the World Health Organization, to draft international recommendations for poliomyelitis vaccine requirements. Those attending were Dr. Roderick Murray, U. S. A.; Dr. O. Bonin, Germany; Dr. D. G. Evans, United Kingdom; Professor S. Gard, Sweden; Dr. J. H. S. Gear, South Africa; Dr. A. Lafontaine, Belgium; Dr. P. Lepine, France; Dr. H. von Magnus, Denmark; Dr. G. Penso, Italy; and Dr. V. Soloviev, U. S. S. R. The recommendations developed by the group were based closely on the United States' experience with poliomyelitis vaccine.

The continued successful use of poliomyelitis vaccine, as well as future developments in the field, may depend on knowledge of the various poliomyelitis viruses prevalent throughout the world and of other viruses causing similar clinical syndromes. The cooperation of national laboratories with World Health Organization regional poliomyelitis laboratories will facilitate the collection, interchange, and study of poliomyelitis viruses, and the exchange for study of viruses which may be responsible for clinical diseases resembling poliomyelitis.

INTERNATIONAL BIOLOGICAL STANDARDIZATION

There are compelling reasons why biological standards should be uniform throughout the world. Experience has shown the difficulties in which physicians, public health services, and manufacturers alike can be involved through the existence of a variety of different units expressing the potency of one and the same drug.

The decision to study the problem of biological standardization internationally was made by the League of Nations' Health Committee at its second session in Geneva, in 1921. Since World War II, the work has been carried forward by the World Health Organization's Section on Biological Standards.

The method of work today is founded entirely on international cooperation, just as it was in the beginning. A national control center is designated in each country to take charge of the international standards and equivalent national standards. The Statens Seruminstitut in Copenhagen is responsible for storage and distribution of international standards for vaccines and antisera. Pharmaceutical substances are maintained at the Medical Research Council's Department of Biological Standards in London.

Last year the World Health Organization initiated a program for the development of international recommended requirements for both the manufacture and the control of biological substances. Adoption of these requirements by national control authorities would promote improvement and greater uniformity in biological products, and would permit free exchange of such substances between nations in times of emergency. So far, recommended requirements have been drafted for poliomyelitis vaccine, yellow fever vaccine, and cholera vaccine. None have as yet been officially adopted.

SOME MAJOR PRODUCERS, CONTROL CENTERS, AND INVESTIGATORS OF BIOLOGICAL PRODUCTS THROUGHOUT THE WORLD

Pasteur Institute, Dakar, French West Africa
The South African Institute for Medical Research, Johannesburg, Union of South Africa
The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia
Oswaldo Cruz Institute, Rio de Janeiro, Brazil
Butantan Institute, Sao Paulo, Brazil
Medical Research Institute, Colombo, Ceylon
Statens Seruminstitut, Copenhagen, Denmark
Lister Institute of Preventive Medicine, London, England
National Institute for Medical Research, Mill Hill, London, England
Pasteur Institute, Paris, France
Paul-Ehrlich-Institute, Frankfurt-on-Main, Germany
Haffkine Institute, Bombay, India
Pasteur Institute of Southern India, Coonoor, India
Central Research Institute, Kasauli, India
Pasteur Institute, Bandung, Indonesia
Pasteur Institute of Iran, Teheran, Iran
Laboratory of Microbiology, Instituto Superiore di Sanita, Rome, Italy
National Institute of Health, Tokyo, Japan
West African Council for Medical Research Laboratories, Yaba, Lagos, Nigeria
State Institute of Hygiene, Warsaw, Poland
Karolinska Institute, Stockholm, Sweden
State Bacteriological Laboratory, Stockholm, Sweden
Queen Saovabha Memorial Institute, Bangkok, Thailand
Biologics Control Division, Central Institute of Hygiene, Ankara, Turkey
Division of Biologics Standards, National Institutes of Health, Bethesda, Maryland, U. S. A.
Institute of Epidemiology and Microbiology, Moscow, U. S. S. R.
Moscow Institute for Poliomyelitis Prophylactics, Moscow, U. S. S. R.

SIGNIFICANCE OF FOREIGN CONTRIBUTIONS TO PRESENT KNOWLEDGE IN THE FIELD OF CANCER

The study of cancer is as old as medicine itself. Some of the earliest written records of human knowledge reveal that men of science and learning were vitally concerned with the cause and treatment of malignant tumors. The accumulation of knowledge about cancer, however, has not been a continuous process. For many centuries, particularly during the Middle Ages, little of value was learned about the nature of cancer, its cause, and treatment. The era of modern cancer research really began less than 200 years ago, at the close of the 18th century.

The period of the 19th and 20th centuries witnessed many fundamental changes in cancer research, as in all of medical science. Great strides were taken in the identification and classification of cancer, knowledge of cancer causation, and treatment. During this period, cancer research became experimental in nature, laboratory animals came into use, the systematic study of disease—pathology—was born and enlarged, and the development of the microscope and other valuable research tools permitted scientists to gain knowledge about the basic unit of life, the cell.

Cancer research continues to expand fruitfully through the contribution of investigators in many countries throughout the world. The United States has made the largest contribution in money, facilities, and trained personnel; but future knowledge and advances are also dependent on the work of scientists in other countries.

In this report the principal discoveries and advances in cancer research, both ancient and modern, are summarized. Although the signifiance of foreign contributions is emphasized here, the work of American scientists in the development of modern cancer research cannot be omitted. The report is concluded with a brief account of the currently important fields of cancer research abroad.

ANCIENT CANCER RESEARCH

Cancer Recognized by Ancient Peoples.—The ancient Indian epic, the Ramayana, 2000 B. C., describes a disease resembling cancer. Five hundred years later, the author of the Ebers Papyrus in Egypt referred to cancerous growths and their treatment.

Ancient Forms of Treatment.—The surgical removal of malignant tumors was widely practiced by Indian physicians 4,000 years ago. Almost equally long ago, Egyptian physicians used an ointment of arsenic and vinegar in treating external cancers. These two forms of treatment were utilized through the ages; and one of them, surgery, remains a proved method of treatment and curing cancer.

Description and Classification of Cancer. Hippocrates, who lived in the fifth century B. C. in Greece, first recognized benign and malignant tumors, a major advance over the earlier Indian and Egyptian

concept that all swellings were cancerous. More than ten centuries later, Paul of Aegina in the seventh century A. D. stated that cancer could arise in any external or internal part of the body, a concept well recognized today.

Early Theories on the Causation of Cancer.—The methods available to ancient investigators seriously hampered their work in the area of cancer causation and led to many unproductive theories. For example, Galen, a Greek of the second century A. D., considered cancer to be a manifestation of the individual's constitution, and this belief persisted almost to modern times. But Galen was nonetheless a skilled investigator who recognized that a primary cancer could give rise to secondary tumors and that the disease must be diagnosed at the earliest possible time.

MODERN CANCER RESEARCH

Percival Pott: The First Modern Cancer Research Scientist.—Perhaps the first accurate description of tumors resulting from a specific, known cause occurred in 1775 when Percival Pott, the English surgeon, related scrotal cancer in chimney sweeps to prolonged exposure of these men to soot.

Cancer: A Disease of Cells.—Marie-Francois-Xavier Bichat, a French anatomist who died in 1802 at the age of 31, recognized that tumors must be composed of cells. Bichat's work was purely theoretical, because his investigations were conducted without the aid of a microscope. Johannes Müller, a Berlin scientist, published in 1838 the first extensive microscopic study of diseased tissue and definitely established the part of the cell in tumors. His classification of tumors was the first to be based on the appearance of the tumor cells.

Virchow and the Rise of Pathology.—Müller's most famous pupil was Rudolph Virchow who sensed the importance of the microscopic approach to pathology. His book, "Cellular Pathology," published in 1858, is one of the most important works in the history of medicine. Virchow's work made possible the accurate diagnosis of cancer by tissue examination.

Chronic Irritation as a Cause of Cancer.—Virchow suggested that some cancer develops as a result of chronic irritation, a theory acceptable today with modification. In 1915 two Japanese scientists, Yamagiwa and Ichikawa, successfully induced tumors on the ears of rabbits after prolonged and repeated applications of coal tar. This was the first case of the production of experimental tumors by the application of a carcinogen (cancer-producing substance), and it lent support to Virchow's chronic irritation theory. The era of experimental chemical carcinogenesis began in 1926 when E. L. Kennaway and his group at the University of London extracted 3,4-benzpyrene, a well known carcinogen, from coal tar.

Systematic Cancer Research in Animals Becomes Possible.—A relatively obscure Russian veterinarian, M. A. Novinsky, first successfully transplanted a tumor from one dog to another. This was accomplished in 1876. Then, at the turn of the century, Carl Jensen, in Denmark, developed a transplantable tumor in rodents, which made it possible for research scientists to study cancer in relatively cheap, small, fast-breeding animals.

Continued Improvement in Cancer Surgery.—Christian Billroth (1829–1894), an Austrian surgeon, was the founder of modern abdominal surgery. His work constituted a new departure in the surgical treatment of internal cancer.

X-Ray and Radium.—Near the end of the 19th century, a new and powerful weapon against cancer was discovered by European scientists. In 1895, the German physicist, Wilhelm Conrad Roentgen, reported the discovery of the X-ray; and three years later, Pierre and Marie Curie isolated the highly radioactive element, radium. These and subsequent advances have provided numerous valuable tools, not only for the treatment of cancer but also for cancer diagnosis and fundamental research on the nature of malignant disease.

Beginning of Research on Viruses and Cancer.—Although some investigators had previously suggested that cancer may be caused by viruses, this idea remained without experimental support until Peyton Rous, of New York, showed in 1911 that a tumor occurring in domestic fowl was caused by a virus. This work lay in relative disregard until only a few years ago when interest in virus studies was revived. Today, virus research is one of the most important areas in the broad study of cancer in animals and man.

Treatment of Cancer with Drugs.—Although efforts to treat cancer with drugs were reported as long ago as 1865, these activities were of relatively little value when compared with the present scope of cancer chemotherapy. The modern era in chemotherapy began in 1941, when Huggins in the United States demonstrated that certain forms of cancer responded favorably to treatment with hormones. Then, during World War II, several American investigators, including Goodman, Gilman, and Dougherty, and Jacobson, found nitrogen mustard, a chemical related to mustard gas, effective in the treatment of certain cancers of the blood-forming organs, particularly Hodgkin's disease. These observations were a great stimulus to further research in cancer chemotherapy. In 1948 Farber in the United States found that chemicals that interfere with the ability of cells to utilize folic acid (a vitamin) could produce complete remissions in acute leukemia in children. This research literally put the theoretical approach to cancer chemotherapy on a practical basis, because it indicated that drugs with the special ability to attack cancer cells could be designed and produced in the laboratory. Today, chemotherapy research is probably the largest single facet in the total scientific effort to control cancer.

Exfoliative Cytology: A New Method for Detecting Cancer.—Two American scientists, Papanicolaou and Traut, reported in 1943 that cancer of the uterine cervix (neck of the womb) could be detected by microscopic examination of fluids obtained from the female genital tract. This technique for cancer detection has been extensively applied and evaluated, and has proved extremely valuable in detecting cases of uterine cervical cancer at a stage when treatment by surgery or radiation is most likely to be curative. Many other scientists are attempting to perfect methods of applying the cytologic test to the detection of cancer of several other internal body sites.

PRESENT CANCER RESEARCH ABROAD

England.—The Chester Beatty Memorial Research Institute in London, under the leadership of Alexander Haddow, is in the forefront of basic studies on the process of carcinogenesis and has one of the most important programs in chemotherapy in the world.

The Imperial Cancer Fund at Mill Hill has been a leader since the earliest days of virus-cancer research.

France.—The Pasteur Institute in Paris with A. Lacassagne and his coworkers has made numerous important contributions in the fields of radiology and the hormonal aspects of cancer. Charles Oberling, Director of the Institute of Cancer Research at the University of Paris, has for many years been deeply interested in the relationship of viruses to cancer.

Italy.—There are Cancer Institutes in Milan, Rome, and Naples. The Milan Institute of Pharmacology is evolving as an important center in cancer chemotherapy research with Garratini as one of the principal investigators.

Germany.—Domagk, who received the Nobel Prize for his discovery of sulfanilamide, is now working on cancer chemotherapy and has introduced a number of new and interesting anticancer compounds. Warburg, another Nobel Prize winner who is often credited with initiating the modern, biochemical approach to cancer research, is continuing to make important contributions in the field of biochemistry.

Holland.—Mühlbock is now chairman of the research commission of the International Union against Cancer. Basic research on carcinogenesis, biochemistry, and virology is being pursued at the Leeuwenhoek Institute in Amsterdam.

Denmark.—Clemmesen is maintaining one of the outstanding and most useful tumor registries in the world. His epidemiological studies of cancer have provided much valuable information on the extent of cancer in Denmark.

Sweden.—The Radiumhemmet in Stockholm is probably the most important single radiation treatment center in the world. Methods of treatment, long-term followup of patients, and fundamental studies on the effects of radiation have been represented among its contributions.

Russia.—The oldest cancer institute in the Soviet Union is in Leningrad and is headed by Serebrov. It specializes in clinical research and in studies of carcinogenesis. In the latter, Shabad has made noteworthy advances. In Moscow, the Institute of Experimental Pathology and Therapy of Cancer, under Blokhin, is the center for experimental chemotherapy. The Russians have a number of able cancer investigators, and it is of interest that the next (eighth) International Cancer Congress is to be held in Moscow in 1962.

Japan.—The Japanese are continuing their significant research on carcinogenesis, genetics, and experimental cancer chemotherapy. Yoshida is perhaps the most influential research worker.

India.—The Lady Tata Institute in Bombay under Khanolkar is a study center for the relationships of environmental factors to human

cancer—for example, oral cancer among betel-nut chewers. Khanolkar is the current president of the International Union Against Cancer.

Better cooperation and more rapid transmission of information, as well as encouragement of the most talented research workers throughout the world, would be extremely useful to the United States in that such activities undoubtedly speed the day of the discovery of the causes and cure of cancer.

PART 2

AN OUTLINE OF INTERNATIONAL COMMUNICATION IN THE MEDICAL SCIENCES

AN OUTLINE OF INTERNATIONAL COMMUNICATION IN THE MEDICAL SCIENCES

INTRODUCTION

Most of the ways used by medical scientists to exchange information about the results of their experimental work are conventional; in 300 years of scientific history there have been few innovations. William Harvey, discoverer of the circulation of the blood, ventured from England to Italy to study under Fabricius; international research fellowships and visiting professorships abound today. The published scientific journal replaced handwritten international correspondence in the 17th century. Today, while there are more scientific journals than ever before, the need to communicate is so great that scientists depend on personal correspondence, mimeographed advance issues, and preprints to supplement the journals. The first international scientific congress dates to 1851; scientists have been using this communication device for over 100 years.

The techniques—foreign study, international congresses, cooperative working committees of scientists, international scientific journals and abstracting services—have not changed appreciably with the years. What has changed is the volume of communications. Increase in the number of researchers all over the world, of their studies, and the publications resulting from them have subjected the systems devised for communication to social and economic stresses. To accommodate this increase in communication volume, scientists and their private and governmental sponsors the world over have sharply increased the number of national and international scientific societies, working committees, symposia and meetings, national and international journals and abstract services.

Concurrently, a need for more coordination has arisen, resulting in the creation of forms which are essentially new. At the scientific level, national scientific societies have formed multi-society amalgamations (American Association for the Advancement of Science, American Institute of the Biological Sciences, Federation of American Societies for Experimental Biology), which hold joint meetings and establish inter-society coordinating committees. At the governmental level, the formation of scientific coordinating agencies is a phenomenon of the postwar years (Centre Nationale de la Récherche Scientifique in France, Consiglio Nazionale della Ricerche in Italy, National Science Foundation in the United States).

Finally, at the international level, there are not only international unions of national scientific societies (The International Council of Scientific Unions, the International Union Against Cancer, the International Union of Biological Sciences), but also new supra-national agencies (WHO, UNESCO), which have both scientific and intergovernmental coordinating responsibilities.

The devices for international scientific communication outlined in this report were created over the years by scientists in order that they might inform themselves freely and quickly concerning developments in specialized scientific fields throughout the world. Financial support for many of these devices (e. g., international congresses) has traditionally come from private sources with occasional governmental subvention. Over the last decades, however, the interests of governments in the social benefits of scientific progress and sharp increases in the volume of scientific communication have created new situations where governments, working through their new coordinating agencies, have assumed more responsibility for the maintenance and improvement of this communication machinery. The governmental agencies of the several countries provide not only financial assistance to scientific societies, but also technical assistance in the planning, improving, and coordinating of the communication machinery.

At any national level, there is an intermingling of scientific, philanthropic, commercial, and governmental interests. The pattern in each country varies with the national traditions, political philosophy and economy, and level of scientific competence of that country.

The outline that follows describes the pattern established within the United States.

OUTLINE

I. International Exchange of Persons.
II. International Congresses and Conferences.
III. International Working Committees.
IV. Science Attaché Programs.
V. International Journals.
VI. Translation Programs.
VII. International Exchange of Publications.

I. INTERNATIONAL EXCHANGE OF PERSONS

Academic, philanthropic, governmental, and supra-governmental agencies all have programs to assist qualified individuals in overseas study and travel (1, 2). In 1955 it was estimated that in all fields 40,000 foreign citizens would study, train, or teach in the United States, and that approximately 20,000 Americans would study abroad.

The level of such study varies widely with the need and background of the scientist. In medical research, the following patterns for study beyond the doctoral level emerge:

A. Private programs

Visiting professorships at universities. Fellowships for foreign researchers at American universities (e. g., Rockefeller Institute of Medical Research). Exchange senior fellowship programs. Sabbatical years for school faculties. These are arranged by the universities, and financed in part by them, by private foundations, and by government programs (e. g., Fulbright Program) (3).

Foundation study grants. A large number of private foundations support the overseas study of qualified researchers (e. g., the Rockefeller Foundation offers 200 fellowships). Voluntary agencies (e. g., The National Foundation) similarly support special investigations overseas.

Privately financed study overseas, while uncommon, is not unknown.

B. Representative Programs of the United States Government

A number of Federal agencies have authorization for the conduct of educational or research personnel exchange programs. Agencies of the Department of Defense, and those concerned with health and medical affairs (Public Health Service, Veterans' Administration, Atomic Energy Commission) also have authorized programs for employing foreign medical scientists.

The role of the Department of State in processing international educational and research fellowship awards is a central one (4). The Department's interests and responsibilities in international scientific communication are extended also to international conferences, official relationships with supra-national agencies, science attachés, and the like (5). The following are representative programs:

Fulbright Program. The program conducted under the Fulbright Act (Public Law 584, 79th Congress) is a principal government effort in support of overseas study for United States nationals. In the academic year 1955–56, there were 38 awards made for lecturing or research in the medical and related biological sciences.

Smith-Mundt Act (Public Law 402, 80th Congress). This act, administered by the International Educational Exchange Service, Department of State, is used primarily to cover tuition and maintenance expenses of foreign students in the United States.

Inter-American Cultural Relations. Under Public Law 355, 76th Congress, the Department of State administers a program for the exchange of graduate students with Latin-American countries.

Other smaller but pertinent programs are authorized by: Finnish Exchange Act (Public Law 265, 81st Congress), Foreign Economic Assistance Act (Public Law 535, 81st Congress), India Emergency Food Aid Act (Public Law 48, 82nd Congress).

NIH Fellowship Program. NIH has active programs for supporting the researches of foreign scientists in the United States. There were 16 fellowships awarded in fiscal year 1958. Under the Visiting Scientist Program approximately 85 foreign scientists are working in United States laboratories at the present time.

Rockefeller Awards. This is a modest program administered by the Civil Service Commission from private funds which enables a small number of Government-employed scientists to study abroad.

Supra-national Agencies

World Health Organization offers approximately 1,000 fellowship for two purposes:

(*a*) Postgraduate study, observation, research.
(*b*) Attendance at group training seminars.

The fellowships are in the area of public health and preventive medicine, and are designed to strengthen the national health services. WHO occasionally arranges for appointments of visiting professors at medical schools.

UNESCO has a modest program of technical assistance fellowships, which includes such study areas as scientific research, scientific documentation, and scientific instruments.

The Pan American Sanitary Bureau conducts a program of fellowships for study and training in the public health field. Some 430 awards in all fields were made in 1956.

II. INTERNATIONAL CONGRESSES AND CONFERENCES

In 1950 there was a total of 119 international societies in the sciences related to medicine (6). A conservative estimate in 1958 would increase this number to 150. Most of these represent affiliations of national member societies, including those of the United States, and most sponsor periodic international meetings or congresses.

In addition to the periodic congresses, there are increasing numbers of one-time meetings, international symposia (e. g., International Symposium on Biology in the Space Age), sponsored by a national society but open to international attendance. Conservatively estimated, the forthcoming international and foreign scientific meetings in the medical sciences from July 1958 through 1961 would total 275 (7). The Council for the Coordination of Organization in the Medical Sciences lists 32 international medical congresses from April–December 1958. None is to be held in the United States.

American attendance at international scientific meetings is difficult to estimate. The Department of State through its Division of International Conferences may name official delegates to represent the United States to certain conferences. The bulk of the attendance, however, is unofficial and personal.

Attendance at international meetings by scientists of the National Institutes of Health in fiscal year 1958 totaled 79.

The planning and operation of international scientific conferences is usually the function of a permanent secretariat or steering committee. The financing of both the secretariat and the conference comes from a variety of private, public, and international sources: subscriptions from the member societies, subventions from industry and government, and from supra-national organizations (WHO and UNESCO).

In the United States, the National Research Council and the Department of State have traditional responsibilities for supporting international scientific meetings. The National Institutes of Health has assisted in supporting such meetings through the making of research grants. Some recent examples of meetings receiving such support are:

Ninth International Congress on Rheumatic Diseases.
Seventh World Congress on Rehabilitation.
Fifth International Congress of Internal Medicine.
First International Congress of the Neurological Sciences.
World Congress of Gastroenterology.
International Congress on Radiation Research.
International Nutrition Congress.

The following is a brief description of the roles played by United States Government agencies in planning and coordinating international scientific meetings:

National Research Council. Office of International Relations. Nominates official delegates to the Department of State, recommends NRC representatives, defrays travel costs, collects and disseminates information.

United States Department of State. Division of International Conferences. Arranges official delegations, defrays travel costs, col-

lects and disseminates information on international conferences in all fields.

United States Department of State. Office of Science Advisor. Maintains overseas staffs. Encourages United States participation in international scientific activities. This office has been newly reconstituted. For a broad policy consideration of the State Department's role in supporting international science, the report of the study group led by Dr. L. W. Berkner should be consulted (5).

National Science Foundation. Gave grants in support of 37 scientific meetings held in the United States in fiscal year 1957. These meetings were open to international attendance. In this same year, the Foundation made 211 grants to American scientists for attendance at 49 international meetings. New legislation authorizing NSF to support international conferences is currently being sought (8).

International Coordination

Both UNESCO and WHO have roles in coordinating the activities and planning the meetings of international scientific societies—the former in basic biological sciences, the latter in health and medicine. They join forces in supporting an operational clearinghouse, the Council for the International Organization of the Medical Sciences (CIOMS).

UNESCO, through its five Science Cooperation Offices (Mexico City, Cairo, Delhi, Jakarta, and Manila) has sponsored international conferences (e. g., Symposium on Pharmaceutical Botany, Lima, 1951), and through a Division of International Scientific Cooperation works with the permanent secretariats of the international scientific societies in helping them to coordinate their plans (9).

The World Health Organization has an active program for cooperation with nongovernmental organizations; there were 40 international societies affiliated with it in 1957 (10). Affiliation authorizes the societies to participate in WHO meetings and to have access to WHO documentation.

The Council of International Organizations of Medical Sciences (CIOMS) acts on behalf of WHO to provide coordination for international organizations. CIOMS, with a budget of $23,750 from UNESCO and $20,000 from WHO, has an active program for coordinating international meetings in the medical sciences, for financing them (in 1957, grants totaling $10,000 were made for 14 meetings), and for disseminating information about forthcoming meetings (11).

III. INTERNATIONAL WORKING COMMITTEES

Continuing and ad hoc committees are a common device for international scientific cooperation. As in the case of fellowships, such committees may be under the sponsorship either of international scientific bodies or of governmental bodies. Various types of such committees are suggested below:

Scientific auspices

Planning committees for international congresses, or continuation committees established to implement their resolutions.

Standing committees established by international scientific societies to conduct their business, to promulgate and maintain standardization

within the discipline, etc. Example: Permanent Committee on Taxonomic Nomenclature of the International Union of Zoological Sciences.

Coordinating committees, which meet during sessions of international congresses, frequently conduct symposia and similar scientific programs on specialized problems. Such coordinating committees may continue their existence by corresponding during the intervals between sessions of international societies.

Governmental auspices

Through such agencies as the National Research Council, Pan American Sanitary Bureau, the World Health Organization, and UNESCO, the United States participates in the work of international scientific committees established by inter-governmental agreements. This type of committee activity is best exemplified by the long list of technical expert committees assembled by WHO, some 36 in 1957, to review and advise on specific disease problems. Generally speaking, intergovernmental committees are more concerned with health control program activities than with the progress of basic research in the sciences.

IV. SCIENCE ATTACHÉ PROGRAMS

The increasing role played by governments in international scientific communication is nowhere better demonstrated than in the postwar development of the science attaché system. The basic considerations underlying that established by the United States are described in the Berkner Report (5). The Office of the Science Advisor, Department of State, places attachés in a limited number of overseas embassies. The function of such attachés is to visit laboratories, attend scientific meetings, and report on developments; and the Department of State undertakes to disseminate these reports to government agencies concerned with science. After several years this program was discontinued and has only recently been reestablished.

In the interim the Office of Naval Research maintained a modest but highly effective program for reporting on international scientific developments (12).

Other Defense Department agencies maintain similar information collection programs, but these are usually more narrowly limited to the technical development interest of the Government service and its contractors.

The United States organized effort is one aspect of a widely used technique to collect and disseminate scientific information through embassies. The British Commonwealth Scientific Office maintains a permanent establishment in Washington with Science Liaison Officers representing Australia, Canada, New Zealand, South Africa, and the United Kingdom.

Similar Science Attachés are attached to a large number of the embassies in the United States, France, Netherlands, Sweden, Switzerland, etc. The function of such attachés is to collect and report to their governments news over a broad spectrum of scientific developments. Interest is understandably concentrated on technology.

The communication techniques listed so far have been those involving the personal contact of scientists or their representatives. There follow several techniques which rely on the printed word rather than

verbal exchange of information. The advantages of print are obvious; it reaches more people and is more permanent. Its primary disadvantage is that it can never be as timely as the spoken word.

V. INTERNATIONAL JOURNALS

Of the 4,500 scientific medical journals published in the world (13), it may be conservatively estimated that 1,000 are international in that they conform more or less to the following conditions: (1) their Boards of Editors are not limited by nationality; (2) they accept and publish scientific papers without regard to national origin, and possibly in a plurality of languages; (3) they are freely exported and internationally used. A number of self-styled international journals do not conform to these conditions, whereas a far greater number of "national" journals do. For example, *Acta Medica Scandinavica* and the *Journal of Biological Chemistry* are truly international despite their national origins.

International scientific journals commonly fall into the following categories: (1) those supported by the international societies such as *Acta Unio Internationales Contra Cancrum;* (2) those supported by national societies or foundations, but of international character; (3) those published commercially.

Since the income collected by international societies is commonly limited to national member groups, and since such societies do not enjoy, as the national societies do, the economic advantage of a "captive" subscriptive list, the journals published by international societies commonly have more financial difficulties. Those published by national societies may depend on their membership to receive the journal as a part of their dues. The commercially published international journals in general, judging from infrequent failures, are in a healthy financial condition.

Time lag in the publication of international journals may reduce the effectiveness of communication. For example, one outstanding neurological journal has a three-year backlog of papers awaiting publication. Such backlogs encourage the distribution of small numbers of mimeographs, preprints used by authors to acquaint their colleagues over the world with their latest work. The preprint system has its disadvantages in that it does not make a scientific permanent record which can be universally consulted at will. Problems of "primary publication" are the subject of continuing study (14).

The function of international secondary publications in abstracting and indexing systems, which synthesize and report the voluminous international literature in given scientific fields, constitutes a specialized problem (15).

The point should be made that such indexing and abstracting systems as Excerpta Medica, Biological Abstracts, Chemical Abstracts, Current List of Medical Literature, Quarterly Cumulative Index of Medicine are extremely effective mechanisms in international scientific communication, and are heavily used by medical scientists all over the world.

VI. TRANSLATION PROGRAMS

According to Dr. John E. Holmstrom, "50 percent of the scientific literature of the world is in languages which more than half the

worlds scientists cannot read" (16). This situation obtains in the medical sciences despite the results of preoccupation for many years with the problem of linguistic barriers and such trends as (*a*) the adoption of English as the standard language for international scientific communication by a number of countries such as Norway, Sweden, Finland, Switzerland, Japan; (*b*) the promulgation of new artificial languages such as *Interlingua;* (*c*) programs for the translation of foreign languages into the language of the country.

In the 19th century, when the bulk of the world's scientific literature was published in one foreign language—German—American scientists were expected as a matter of course to acquire facility with this language. As foreign language contributions acquire more significance, and as medical school curricula become ever more crowded with scientific courses, the predicament of American medical scientists facing a voluminous foreign language literature is desperate. It is against this background that governmental scientific translation programs have been created (17).

While accidents of history focused attention on Russian scientific achievement, a more properly balanced estimate of scientific need would assign comparable weight to scientific contributions from other countries such as Germany, Japan, and Communist China. Funds under Public Law 480 have been made available for translation purposes, and governmental translation programs may be expected to broaden their bases.

VII. INTERNATIONAL EXCHANGE OF PUBLICATIONS

Through the years one of the most effective but unadvertised means of international scientific communication has been the free exchange of scientific publications (18). Motivation for this has been twofold: first, the age-old tradition of an "international comity of scholars," not unmixed with prestige motives, has developed this communication technique as a classic method for exchanging information on the results of research; second, where the volume of such exchange has caused the activity to be institutionalized, libraries acting for scientists have an additional motivation of building their research collections.

Exchange of currently published journals

The editorial offices of scientific journals, and the societies which publish them, commonly set aside a number of copies of the journal for exchange with other editors of journals overseas. This mechanism serves to alert the editors who have a public responsibility to the scientific discipline to new advances reported by their foreign colleagues. Such exchanges result in news notes, editorials, translations, or even in the duplication of experimental work.

Where the editors are attached to academic institutions and the volume is large, such exchange activity is commonly conducted by the institution's library on behalf of the editorial office. This results in the building of a permanent collection of scientific literature.

Dating back to the founding of the Smithsonian Institution, the United States Government has recognized the significance of this exchange activity to scientific development in the United States. The Library of Congress is authorized to execute a series of exchanges with

foreign academies of sciences, and other international exchange agreements established by law. Other Federal departments and their libraries similarly have set up exchange programs for scientific literature. The Smithsonian Institution's Office of International Exchange has a traditional role in collecting materials from scientific societies, libraries, and Government agencies—materials to be shipped on exchange—and in consolidating and forwarding these shipments.

Exchange of Reprints

Commonest of practice in international scientific communication is that used by the individual scientist in requesting a reprint of a paper published by an overseas colleague. In formal publication a scientist orders a sufficient number of copies of reprints to distribute to his colleagues, and a supply with which to service mail requests. The volume of this personal communication is incalculable. This universal practice was affected by regulations governing the export of scientific and technical information. The National Institutes of Health bases its policy of nonrestriction of reprint exchange on a Presidential statement encouraging the free exchange of scientific information with Iron Curtain countries.

Exchange of Back Files of Journals

The libraries of scientific institutes over the world acquire large numbers of duplicate scientific journals surplus to their needs. This represents both a major potential resource, and a major problem in logistics.

During the restoration of research libraries following World War II, private financing demonstrated what might be done with funds for this purpose. The American Bureau for Medical Aid to China collected from these sources and sent to the China mainland vast supplies of journals. The Medical Library Association, with a modest grant from the Rockefeller Foundation, collected from its members tons of scientific journals needed by the devastated libraries in Japan. This source was also tapped for the restoration of the medical library at Santiago de Chile following a disastrous fire.

The U. S. Book Exchange, Inc., a nonprofit national exchange center with a stock of over 2,000,000 pieces of surplus scientific literature represents a major resource (19).

Point IV Funds were secured for the shipment of surplus literature. This support has been continued by grant from the United States Information Agency. Despite this aid, a large logistical problem remains in realizing the potential of this agency for international communication.

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PART 3

A BRIEF HISTORY OF AMERICAN MEDICAL RESEARCH

A BRIEF HISTORY OF AMERICAN MEDICAL RESEARCH

Organized medical research in the United States began with the opening of the Johns Hopkins Medical School in 1893, according to Sigerist (American Medicine, W. W. Norton & Company, Inc., 1934). Almost the same date, 1895, is chosen by another historian, Shryock (American Medical Research, Commonwealth Fund, 1947), as marking the beginning of what he calls the fourth epoch of American medical research—its emergence from colonial status to approach its present level of independence.

Three earlier epochs are described by Shryock. The first, from mid-18th century to about 1820, was marked by influence of the British. The second, lasting until about 1860, was influenced by French methods and teachings. And from 1860 to 1895, the German influence gave the inspiration for most medical research in America.

Before 1820 very little was accomplished in medical research in this country, although progress in the physical sciences was significant and valuable observations were made in taxonomy. Lack of facilities and support hampered medical research during this period and for some time thereafter. Physicians were dependent on practice for a living. Those who studied abroad and saw research carried on in European countries were, for the most part, unable to engage in such unprofitable and ill-appreciated activities on their return to America.

Medical schools were founded, but they were for the training of practitioners. Medical societies and journals came into existence, but again the emphasis was on practice. As Sigerist points out, there were no centers of learning which could in any way compare with those in Europe. Above all, there was missing "intellectual resonance, a mutual reverberation of ideas. Whoever gave up money-making to live for science was considered a crank."

It should be pointed out here that while European influence on medical research in America was relatively short-lived before the last part of the 19th century, European contributions to medical and health knowledge and practice were strongly influential. Sigerist explains the time-lag in the development of research in America along the lines of that in Europe as follows:

> In every country which has been opened to western civilization, we can distinguish three successive stages in its relation to medicine. During the first stage, the population is indeed ready to accept treatment from academically-trained physicians, but the means and the teachers to train these physicians do not as yet exist. They must either be imported, or the native sons must be sent abroad to study.
>
> In the second stage, the point has been reached where this training can be undertaken at home. The number of physicians has increased. Many of them keep in constant touch with scientific progress abroad, make this knowledge their own, and pass it on to their pupils. But it is as yet beyond their compass to undertake independent scientific work, to attack problems of medical research on a large scale. To be sure, we find at this stage individual men who are in advance of their time, but these are isolated examples and are moreover handicapped by lack of necessary equipment.

In the final stage, research work has been introduced and is being pursued with greater and greater intensity. In the beginning, the assistance of foreign scientists, or native scientists educated abroad, will still have to be called upon, till there has been time to train a new generation to take their places.

Only when a permanent institute of research has been established, can medicine be really said to have taken root. Science is the living source from which the practice of medicine derives its daily sustenance. If the source is too distant, practice becomes parched and devitalized. Every physician and every medical institution ought to keep in constant touch with scientific research. To stand still is to regress.

America, too, has advanced along this line of development. In colonial times and even in the nineteenth century, medical students went abroad for their academic education. Then followed the founding of countless schools for the training of practitioners. Finally, with the opening of Johns Hopkins Medical School in 1893, there was established a scientific center of the first rank and with it the beginning of organized research.

From this moment America ceases to be merely a passive recipient of knowledge. It takes its place in medical science. It begins to collaborate in the solution of medical problems. Slowly at first, but always faster and faster, the process of evolution unfolds. Young men are embracing research with overwhelming enthusiasm. And today America is beginning to pay its debt to Europe.

These lines were written in 1934. In the last two decades, American medicine has gone far toward paying its debt to Europe, and the flow of students has reversed itself, turning in the direction of the United States.

Individual physicians in America all through the pre-1893 period did make valuable contributions. In the earliest period, these were often made under great difficulties. Notable were the investigations of William Beaumont, U. S. Army surgeon, who first studied the process of digestion in the human stomach. A report of his findings, published in 1833, has become a classic. Beaumont was astute enough to take advantage of what has been called a lucky accident—that of having cared for a patient with a gunshot wound of the abdomen which failed to close. Heretofore studies of digestive processes had been made on animals. Although working in the backwoods, with a patient who ran away time and again, Beaumont was able to discover that the human stomach secretes mucus and gastric juice and to observe the gastric movements. He noted that digestion is influenced by psychic occurrences to a great degree, learned the effects of tea, coffee, and alcohol on digestion, and studied the digestion of individual foods.

Most of the contributions of the century were in the realm of practical medicine, especially of surgery. The technical skill which characterizes Americans led naturally to the development of surgeons and to appreciation of their accomplishments by a people unusually able to understand technical developments, and unusually impatient for quick results.

Yet, so far as research goes, when John Billings in 1876 wrote *A Century of American Medicine*, he was able to describe the total achievements of scientific study in a single chapter.

The early English influence, according to Shryock, seems to have become somewhat of a handicap to progress in medical research in America. It imbued its followers with the idea of systematizing pathology and therapeutics. Since knowledge in these fields had not progressed enough for real systematizing of the kind that was then proving useful in the physical sciences, the result was a return to

speculative pathology. Yet the English influence did lead to the founding of various colleges of physicians and surgeons and the academies of medicine in cities. These became centers of learning and forums for scientific discussion.

About the mid-18th century, instruction in anatomy was introduced. According to Sigerist, the "first scientific departments in America were institutes of anatomy." One of the early American anatomists was Caspar Wistar (1761–1818), whose collection formed the nucleus of the Wistar Institute of Anatomy and Biology at the University of Pennsylvania. Some of the early students of anatomy turned to surgery. Others, like William E. Horner and Joseph Leidy, turned to pathological anatomy. Leidy made important investigations in anatomy, zoology, botany, paleontology, and above all, parasitology. His most important contribution was the discovery of the trichinosis organism in hogs. Leidy has been called a fine type of the German-American physician—modest, unassuming, learned, and versatile.

The German influence, coming during the last part of the 19th century, was probably the strongest influence on American medical research. American medical men who earlier had flocked to the clinics of Paris turned to German laboratories where they could learn the new methods in experimental physiology, bacteriology, and pathology.

It was after a year of study in the German as well as French laboratories that young Joseph Kinyoun returned to found the laboratory which has subsequently become the National Institutes of Health, the Federal Government's largest organization for the support and conduct of medical research. Kinyoun's first laboratory of bacteriology was set up primarily to facilitate control of infectious disease and to prevent importation of such disease from abroad. His study in Germany had convinced him, however, that such a laboratory was needed not only for aid in detection of disease but also for research to improve methods of disease control.

The history of American medical research cannot be told without relation to social and economic factors. Reference has been made to the emphasis on practice, both because of the physician's need to practice for a livelihood and because of the people's need for therapy and for application of such preventive methods as were developed abroad. Medical research in the early years in America also suffered from lack of facilities and from lack of encouragement and financial support. Shryock points out that even by 1820, and certainly before the war years of 1861–65, there was sufficient wealth in the Nation to have supported some medical research. But in a Nation of essentially practical-minded people, what did it matter that Gerhard, returning to Philadelphia from study in Paris, was able (1837) to distinguish for the first time between typhoid fever and typhus? His inspiration for this early American "first" undoubtedly came from his study abroad. But since, at the time, there was neither cure nor prevention for either disease, the results of his careful studies failed to impress many of his fellow practitioners, much less the rank and file of his fellow countrymen.

Government support of medical research, extended early in the German principalities and in France, did not develop in America until

much later, though there were occasional prizes offered by State governments for the "cure" or "prevention" of some disease. Such private support as was given for research tended to be more for what we would call today "research and development." Again in line with the national insistence on practical and profitable results, studies were largely oriented toward improvement and expansion of physical and engineering developments—particularly important during settlement and development of new parts of the country and the growth of new business and industry.

During the mid- and late-19th century, government and pharmaceutical support of medical and biological research had a small beginning. Progress in analytical chemistry and experimental pharmacology had led to manufacture of ether, quinine, morphine, and strychnine by a Philadelphia firm in the early part of the century. The stimulus of Civil War needs encouraged local druggists to produce extra supplies and thus led to the large drug houses, many of which are still operating. In 1866, Shryock reports, Dr. W. C. Abbott of Chicago found fluid extracts of plant materials unreliable and began to study the work of Belgian dosimetrists and to isolate pure alkaloids—doing all of this in the family kitchen. In the 1890's developments in chemistry and bacteriology opened to the pharmaceutical houses, already approaching the scale of big business, the prospects of applied research in biological products and chemotherapy.

Early support of biological sciences by the Federal Government came with funds provided by Congress for the land-grant colleges (1862) and subsequently for research grants to state agricultural stations in connection with these colleges and the Department of Agriculture. Although this support was primarily for the advancement of agriculture through improvement in methods of farming and animal husbandry, these beginnings included studies in animal and plant pathology. They provided opportunity for such investigators as Theobald Smith, noted for discovering that Texas cattle fever is transmitted by ticks, and for the mold researches which, at a much later date, made possible the large-scale production of penicillin.

Federal support for medical research was also supplied after 1875 through the Army and Navy. Each of these had funds for protection of the health of military personnel, and some of this money began to be used for original studies.

The founding of the Johns Hopkins Medical School in 1893 marked not only the beginning of organized medical research in America but also the beginning of a new kind of support for medical research—that of private philanthropic endowment. In 1901 the Rockefeller Institute for Medical Research was established. Other medical research institutes followed in rapid succession—the McCormick Institute for Infectious Diseases in Chicago in 1902, the Carnegie Institution of Washington in the same year, and the institutes founded by Henry Phipps for research in tuberculosis (Philadelphia, 1903) and for psychiatric research (at Johns Hopkins in 1913).

Other endowment funds were established and, while these did not create institutions on their own account, they contributed considerable annual funds for medical purposes including research. Among these are the Milbank Memorial Fund, Julius Rosenwald Fund, and Com-

monwealth Fund. The Rockefeller Foundation, though independent from the Rockefeller Institute, has also contributed to medical research through its International Health Division.

In the 20th century, also, private philanthropic support for medical and health research in America was obtained through the large voluntary health agencies, such as the National Tuberculosis Association, American Cancer Society, American Heart Association, and National Foundation for Infantile Paralysis. These organizations represent a peculiarly American way of attacking a health problem.

Individual contributions, in the form of gifts and bequests, to universities and medical schools were also made in support of medical research as well as of education.

In the early 1930's, the depression affected not only many private fortunes but also many of the endowment funds. Funds for medical research consequently dwindled. However, the interest of the people in medical research and their growing appreciation of its value, both practical and humanitarian, led to increasing Congressional action for research support. In 1937 Congress authorized the National Cancer Institute with an initial appropriation of $750,000 for a suitable building and facilities. It further authorized annual appropriations of $700,000 to carry out the purpose of the act which was primarily to aid and support research relating to the cause, diagnosis, and treatment of cancer.

World War II brought home to a Nation already growing research-minded the value, and indeed necessity, for further support of research and research training. During the war years, support was primarily for military research and development, with support of medical research concentrated largely on problems related to the health of the military, practical nutrition, and development of domestic sources of drugs formerly imported, such as antimalarials.

In 1940, just before the war, total national expenditures for medical research totaled $45 million. The sum had increased to $330 million by 1957. A large part of the increase, $186 million, was in Government support, though industry, endowment, and philanthropy continued to contribute sizable amounts.

Government support of medical and biological research now comes from the Department of Health, Education, and Welfare, Department of Defense, Atomic Energy Commission, Veterans' Administration, and National Science Foundation.

Since its coming of age in the closing years of the 19th century, American medical research has made progress worthy of the influence and stimulus it received from European research in earlier years. Its contributions chronicled in the following pages have advanced the health not only of Americans but of all mankind. American humanitarianism, which has paralleled American commercialism throughout the Nation's history, has inspired a desire to spread the benefits of medical research throughout the world. At the same time, American medical scientists have continued their visits to European clinics and research centers, not only as students but as teachers, so that medical research now proceeds on a two-way international highway of advancing knowledge.

SOME LANDMARKS IN AMERICAN MEDICAL RESEARCH

1721. Philadelphia Hospital founded.
1735. Medical Society in Boston founded.
1743. American Philosophical Society founded.
1762. First medical library in the United States (Pennsylvania Hospital).
1778. First American pharmacopoeia published in Philadelphia.
1780. Benjamin Rush describes dengue.
1809. McDowell performs ovariotomy.
1833. Beaumont experiments on digestion.
1837. Gerhard differentiates between typhus and typhoid fevers.
1842–46. Long and Morton introduced ether anesthesia.
1843. O. W. Holmes points out contagiousness of puerperal fever.
1849. Marion Sims operates for vesico-vaginal fistula.
1861. E. B. Wollcott first excises renal tumor.
1875. Weir Mitchell introduces rest cure.
1886. Fitz describes pathology of appendicitis.
1887. First research laboratory of Public Health Service, at Marine Hospital, Staten Island.
1893. Johns Hopkins Medical School opened.
1898. Theobald Smith differentiates bovine from human tubercle bacilli.
1899. Reed and Carroll establish transmission of yellow fever by mosquitoes.
1901. Rockefeller Institute for Medical Research established.
1902. McCormick Memorial Institute for Infectious Diseases.
1903. Carnegie Institution of Washington.
1904. Atwater invents respiration calorimeter.
1906. United States Food and Drug Act.
1908. Ricketts discovers rickettsiae, cause of Rocky Mountain spotted fever and other diseases.
1911. Carrel investigates extravital culture (beginning of tissue culture).
Cushing describes dyspituitarism.
Peyton Rous transmits sarcoma by means of a filtrable virus.
1912–1916. Cannon investigates effects of adrenal secretions on emotions.
1920. Goldberger demonstrates dietary deficiency cause of pellagra.
1922. Spencer develops Rocky Mountain spotted fever vaccine.
1926. Minot and Murphy introduce raw liver diet for pernicious anemia.
1937. Congress authorizes National Cancer Institute, first of the National Institutes of Health, at Bethesda, Md.
1938. Caries-inhibiting effect of flourides in drinking water of children demonstrated.
1939. Gross performs first heart operation for repair of congenital defect.
1940. Link discovers the anticoagulant, dicumarol.
Waxman develops streptomycin.

1941. Hormones introduced for treatment of cancer.
1942–1952. Development of synthetic antimalarials.
Introduction of DDT in malaria control.
Fractionation of blood.
Introduction of radioisotopes in tracer studies of metabolism.
1948. Steroids introduced for treatment of rheumatoid arthritis.
1953. Study of molecular diseases.
1954. Polio vaccine.
1957. Public Health Service (NIH) fellowships extended to scientists of foreign countries.

PART 4

PRESENT PROGRAMS OF THE UNITED STATES PUBLIC HEALTH SERVICE INVOLVING INTERNATIONAL RESEARCH

INTERNATIONAL ASPECTS OF RESEARCH IN THE BUREAU OF STATE SERVICES

Some of the research being carried out in the Bureau of State Services that is related to international health is represented here in three major categories.

RESEARCH IN COLLABORATION WITH FOREIGN INVESTIGATORS

Many activities are carried out in collaboration with foreign scientists. The degree of collaboration runs the gamut from informal exchange of findings to cooperative field investigations. Presently, scientists from the Arctic Health Research Center are carrying out field studies on human physiology in the cold climate, in collaboration with Canadians and Norwegians.

RESEARCH OCCASIONED BY THE NEEDS TO CONTROL DISEASES IN THE UNITED STATES

These studies relate to the migrations of animals that are suspected transmitters of disease, and to enterprises undertaken jointly with neighboring countries on the transmission of diseases of mutual concern. Two years ago scientists from the Communicable Disease Center, BSS, visited Guatemala to obtain specimens of migratory birds to determine their role in the transmission of viruses, particularly that of equine encephalomyelitis. Joint studies with Canada have been primarily concerned with shellfish sanitation occasioned by a reciprocal certification program.

RESEARCH PERFORMED AT THE REQUEST OF INTERNATIONAL AGENCIES

Research may be undertaken because of formal requests or because of informal expressions of interest by international organizations. As early as the 1920's, the League of Nations asked for Public Health Service collaboration in studies on the serology and treatment of syphilis.

At the request of the World Health Organization, centers for influenza and *Shigella* have been established at the Communicable Disease Center to serve the Americas. These centers not only collect data with respect to the Americas but serve as reference laboratories for specimens shipped from abroad.

CDC has collaborated with the Pan American Health Organization in studies made along the Mexican border with respect to the epidemiology and control of rabies, and through the loan of personnel, has assisted PAHO in investigations to determine the efficacy of specific insecticides for malaria eradication programs.

At the request of UNICEF, studies were made in Puerto Rico of a diarrheal outbreak transmitted in dried-milk preparations that UNICEF is purchasing and distributing throughout the world.

At the request of ICA, studies have been undertaken on the development of insecticides and their method of application. Also at the request of ICA, a team of epidemiologists was sent to Pakistan to study an outbreak of smallpox and determine methods for its control.

BSS participates in the studies of AEC made by the Atomic Bomb Casualty Commission. PHS recruits and employs scientists for assignment in Japan and provides a member of the Advisory Committee of the Commission.

MEDICAL AND HEALTH RESEARCH OF INTERNATIONAL SCOPE IN THE BUREAU OF MEDICAL SERVICES

RESEARCH IN LEPROSY

At the United States Public Health Service Hospital in Carville, Louisiana, the sulfone drugs were first tried against leprosy in the early 1940's. The sulfones soon supplanted chaulmoogra oil as the "treatment of choice" for this ancient chronic disease. Today physicians throughout the world agree that these drugs offer a comparatively effective form of treatment. Every year doctors, nurses, scientists, and others working in leprosy throughout the world come to Carville to observe treatment and learn the procedures used there.

The sulfone drugs work slowly and are not effective in all cases. The search still continues for a faster acting specific remedy. During fiscal year 1959, the sum of $84,000 has been earmarked for research in leprosy.

NARCOTIC ADDICTION

Each year many physicians and others visit the PHS hospitals at Lexington and Fort Worth to learn about the treatment of addicts. Visitors have come to the hospitals from Sweden, Hong Kong, Australia, Thailand, the Philippines, and many other locations.

TRACHOMA MANUAL AND ATLAS

During the past year, the Division of Indian Health made a unique contribution to international medicine through the publication of the *Trachoma Manual and Atlas.* Although trachoma seldom occurs in the general population of the United States, many cases have been found among the Indians within the past two years. Since there is no recent instructive material on the disease from which physicians may learn about it, the *Manual* was written for the use of the medical staff of the Indian Health service. Since publication, it has attracted wide attention in other countries, and a request has just been granted for translation into French. Trachoma is still a serious menace to health in many countries of the world.

DENTAL RESEARCH TECHNIQUES

During the past two years, several publications and professional papers on the work of the Division of Dental Resources, particularly the research techniques developed by the Division, have been trans-

lated by non-Government organization into Spanish for distribution in Latin American countries. The Division also receives many visitors from other nations who wish to learn about various aspects of research in the field of dental resources.

INTERNATIONAL COOPERATION IN NURSING

There are three kinds of services which the Division of Nursing Resources is requested to give in relation to international health programs and activities. One of these activities involves participation in overseas programs. For the last two years the Division has been requested to provide a special consultant to direct or guide international workshops on nursing research or survey methodology.

In November, 1956, Miss Margaret Arnstein was the director of the International Conference on the Planning of Nursing Studies held at Sevres, France. She was on loan to the Florence Nightingale International Foundation for a period of three months to prepare for and direct the conference and assist in writing the final report.

Mrs. Apollonia Adams was requested by the World Health Organization to assist in the workshop on survey methodology held in Brazil in July 1958, and to assist the Brazilian survey committee in analysis of some of the data which they had collected in making a nationwide survey of nursing in Brazil. This particular workshop was sponsored not only by the World Health Organization but also the Brazilian Nurses' Association and the Ministry of Health of Brazil.

Neither one of these workshop activities required any travel or per diem funds from the Public Health Service. Miss Arnstein was on leave without pay for the three months. Mrs. Adams' salary from the Public Health Service continued while all other expenses were paid by the World Health Organization.

The second activity is the giving of field experience, usually short term, to those foreign nurses who wish to spend time working in the Division with the staff and learning more about the details of research and survey methodology. To date, such field experience has usually been of a month to six weeks' duration. Within the past two years one nurse from Portugal, one nurse from Brazil, and one nurse from Chile (who is now a consultant for World Health Organization in Argentina) have had this field experience with the Division.

Finally, the Division receives several visitors from other nations each month, both nurses and physicians, who come to learn about the nursing research activities of the Public Health Service and about nursing research throughout the United States.

The Division also conducts a continuing exchange of information in the field through its own resources and through the International Council of Nurses and the World Health Organization.

INTERNATIONAL RESEARCH ACTIVITIES OF THE NATIONAL INSTITUTES OF HEALTH

The activities in international research of the National Institutes of Health comprise a broad range. Employing some $3,619,671 from grants and direct operations funds of fiscal year 1958, NIH participation is most intensive in two areas: support of research abroad and

of interchange of scientific personnel. These two accounted in 1958 for about $2.9 million of the total $3.6 million. Other activities, such as aid to scientific information interchange and to international scientific assemblies, are considerable and are growing. Cooperation with World Health Organization is developing strongly.

Stemming from the obligations of PHS legislation, scientific activities are carried out by NIH as the Service's research arm. The summaries and descriptive narrative that follow sketch the nature and extent of present NIH international programs. All figures are estimates and involve fiscal year 1958 funds.

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1. INTERCHANGE OF SCIENTIFIC PERSONNEL

Through NIH-supported programs, medical research with emphasis upon training values is conducted by American scientists abroad and by foreign scientists in this country. Four programs are involved: the visiting scientist program, the guest worker program, research fellowships, and foreign fellowships. These make up a relatively small but highly significant part of the overall training activities of the Institutes.

The visiting scientist program, established in 1950, is a flexible arrangement for inviting outstanding American and foreign scientists with very special qualifications to participate in the utilization of NIH laboratory and clinical resources. Participants must have a doctoral degree or the equivalent background, at least six years of postgraduate experience, and exceptional ability in a specific research area of importance to the programs of the NIH. The purpose of the program is to increase the utility of NIH as a national resource, to strengthen relations with the broader scientific community, and to advance particularly complex research. Among the visiting scientists from a total of 34 foreign countries have been three Nobel prize winners. Presently, over 80 visiting scientists are participating in the program. Fiscal year 1958 funds for this program totaled $534,000.

The guest worker program, though less formalized, has brought many eminent investigators to NIH. In these cases, the laboratory and clinical facilities of the Institutes are made available to workers

whose home institutions provide partial support. A major benefit to scientists in this country has been the opportunity to learn recently developed and valuable techniques and to evolve work programs in consultation with both domestic and foreign nationals of eminence. There are 18 foreign guest workers at NIH at the present time. They receive no salary or stipend from NIH.

Research fellowships enabling scientists from the United States to study in foreign countries were first awarded in 1947. These fellowships are made to candidates having an M. D., Ph. D., D. D. S., or equivalent degree. The fellow is permitted to study at the institution of his choice, usually for a period of a year with opportunities for extension. The awards are made on a competitive basis upon recommendations by scientific committees. Such fellowships have not been numerous, amounting to only 300 from 1947–1957. In 1958, NIH supported 86 American research fellows studying in 11 foreign countries. The funds employed totaled $452,097.

Postdoctoral research fellowships for citizens of other countries were reestablished on a limited basis in fiscal year 1958. Experience with such long-established activities as the Belgian and Scandinavian fellowships has shown that there is no more effective way to leave a sharp and true image of this country and its scientific effort in the minds of the intellectual leaders of a nation than to have them live and study in the country. Moreover, the laboratories of many countries in Europe have regained a position of world leadership, and the leading younger medical and biological investigators from these laboratories have much to bring to this country. Among requirements are the doctoral degree or its equivalent, a demonstration of outstanding research promise, nomination by the leading medical research organization of his own country, and acceptance by the laboratory in the United States at which the candidate proposes to train. Seventeen traineeships and training grants for fellowships in United States research were awarded from $90,797 of fiscal year 1958 funds.

2. INTERNATIONAL SCIENTIFIC ASSEMBLIES

Among the most valuable of the mechanisms furthering international exchange of scientific knowledge are the general scientific assemblies which bring together outstanding scientists from all over the world to meet, present scientific papers, and discuss the current state of knowledge and probable future lines of productive inquiry in a given area of science.

As the barriers between nations have been progressively demolished, and as the geographic and substantive dimensions of science have grown, these international meetings have become an invaluable and irreplaceable facet of scientific communication. They encourage both the exchange of information and the discussion and planning of collaborative studies. In addition to the professional benefits derived from such meetings, they contribute to international understanding and good will in that they represent an act of scientific fraternity devoid of nationalism, and provide the scientist with an opportunity for exposure to the customs and culture of other lands.

For the most part, these international assemblies are held under the auspices of a professional international society, association, or union. They are planned so that various countries in sequence can serve as a

host at the same time as the international communication needs of the scientific group are met.

As Public Health Service support of medical research has emerged in recent years, it has been apparent that its advisors believe in utilization of a portion of appropriated funds for research and training in order to defray at least a portion of the total cost of developing effective international exchange of information in the scientific fields in which the Institutes have special interest.

At the present time, through National Institutes of Health appropriations, support is provided for international scientific assemblies in two basic ways.

First, on the basis of applications made to the Institutes by the sponsoring group and reviewed by Advisory Councils for their relative contribution to a given scientific field, grants are awarded by the Surgeon General to defray a portion of the cost of organizing and carrying out the broad intent of specific international scientific assemblies. Such grant funds have in the past been used to provide travel funds for scientists invited to participate in the meeting, to cover program planning, administrative costs, or publication of proceedings. In fiscal year 1957, fifteen international meetings were partially supported in the amount of $110,000. In fiscal year 1958, ten such meetings were partially supported in the amount of $85,909. Typical of the professional groups receiving support were the International Union Against Cancer, International Congress of Cardiology, World Congress of Gastroenterology, and International Congress on Nutrition.

Second, NIH appropriations have been used to provide indirect support of international assemblies through the grantee's use of a portion of his research grant funds to pay for travel to such meetings. This is done at times by provision for such travel in the grant application. More often, in the course of grant-supported research, the grantee is specially invited to present a paper on his work at an international meeting. With the recommendation of an Advisory Council and approval by the Surgeon General, research grant funds may be used for this purpose. In fiscal year 1958, about 150 grantees attended international scientific meetings under these circumstances, supported in part by funds totaling approximately $100,000.

In addition, during fiscal year 1958, approximately 100 NIH scientists attended over 50 international meetings, at an estimated cost from NIH funds of $50,000.

3. INTERNATIONAL RESEARCH ACTIVITIES

International research, for this purpose, is defined as research done outside the United States and its Territories. Excluded under this definition is the substantial volume of research conducted in this country which obviously has international significance insofar as it is productive and its results are widely disseminated throughout the world.

There are two major ways in which NIH programs have provided support for research that is conducted in other countries. The first of these is through research grant support.

A limited number of grants are made to foreign nationals. It is evident that research grant funds are intended primarily for sup-

port of research by United States scientists and carried out within the United States. On the other hand, it is clear that there are circumstances under which it is to the best interests of the American people as well as of science for these funds to be used in support of non-United States studies. By statute, the fundamental scientific and program recommendations on which projects shall be supported rests with the Advisory Councils. These advisors, supported by the advice of Study Sections and working with Public Health Service staff, have evolved in practice a set of general criteria against which research grant applications submitted by foreign nationals are measured. Suitability of such a grant is inquired into in terms of the uniqueness of the research opportunity, the special qualifications of the investigator, the characteristics of his research environment, the merit of the project application, and the total need for the data to which the project is directed.

Grant applications from non-United States scientists are screened carefully by PHS advisory groups from their points of view. Under these circumstances, only a small percentage of the appropriated research grants funds are awarded to scientists in other countries. In 1957, NIH appropriations supported 58 research project grants in the total amount of $814,600. In 1958, this increased to 96 projects at a total cost of $1,443,142.

In addition to the support of research by grants, the Public Health Service also conducts as part of its own direct activities certain laboratory and field studies which are carried out in other countries. These are treated as direct extensions of its own laboratory and clinical studies in this country.

The establishment of such field laboratories and studies takes place only after careful assessment, among other things, of the potential values of the studies, the degree to which they relate to continuing research interests in the Bethesda and other laboratories, and the international scientific and governmental relationships involved. In the past, these direct offshore research operations have included, for example, the field study of filariasis in Tahiti, the study of the control and treatment of onchocerciasis in Guatemala, the demonstration in Egypt of the use of chemicals to control snail populations that are host to the organism of schistosomiasis, and research on the several tropical diseases that are endemic in Liberia.

In such studies, and particularly when they involve the construction or modification of laboratories, the opportunities and obligations for collaboration with other government research programs are many.

Included in the direct support of research, too, is the extensive international exchange of infectious organisms, biologics, and chemicals between scientists at NIH and scientists in academic, government, and industrial laboratories all over the world. The Division of Biologics Standards, for example, supplies reference standards and reference sera and vaccines to foreign governments on request. Steroid chemicals, analgesic drugs, analogues of vitamin B12, and other chemicals are exchanged; and a substantial number of chemicals in the cancer chemotherapy program are received for screening in animals and for clinical trial in men.

In current direct research operations outside the United States, there is a new development in the establishment in Panama of a

small and temporary field station to further research in diseases of importance in the tropical Americas, such as the arthropod-borne viral infections and fungal diseases. This project was developed in collaboration with the Department of the Army and with the support of the Government of Panama. Known as the Middle American Research Laboratory, this was supported with $124,000 from fiscal year 1958 funds.

4. INTERCHANGE OF SCIENTIFIC INFORMATION

There is general agreement (*a*) that there is immediate need for better and faster communication of the scientific literature of all nations; (*b*) that language differences will continue to be one of the primary barriers to scientific communication in the foreseeable future; (*c*) that effective translation programs, with the product widely disseminated, can aid materially in reducing the international communication problem; and (*d*) that the Public Health Service bears a major portion of this country's responsibility to facilitate the translation and dissemination of scientific literature in medicine and biology for the benefit of American scientists everywhere.

American medical scientists' missions to Russia have observed that Soviet scientists in general are more abreast of American developments in the medical and biological sciences than is true in reverse. Consequently, Congress in 1957 directed the National Institutes of Health "to provide, through grant or contract, a Russian medical research translation service," and authorized $233,000 for the program during that year. It continued at essentially the same level during fiscal year 1958.

The program was designed to supplement and complement existing activities and to meet certain of the more apparent needs of those engaged in a wide variety of bio-medical sciences, both basic and clinical, through publication and distribution of selected Russian translated journals, abstracts, reviews, informational directories, compilations, and guides. The program is now in its second year and has progressed soundly.

In addition to the Russian scientific literature translation and dissemination program, NIH is also assisting in the interchange of medical and biological research information in other ways. Principal among these is the provision of grant support, upon recommendation of the National Advisory Councils and approval of the Surgeon General, Public Health Service, for means and methods of improving and increasing the interflow of medical research findings. In this area, for example, grants have been made to the Excerpta Medica Foundation for the initiation of abstracting journals, covering the world literature, in three fields of current especial interest and importance—cancer, cardiovascular diseases, and gerontology. Though modest in extent and number, this area of aid for scientific information interchange appears worthwhile in helping to fill gaps and complementing established mechanisms. Three grants, totaling $50,945, were made for this from 1958 funds.

5. COOPERATION WITH WORLD HEALTH ORGANIZATION

WHO and the Public Health Service's NIH cooperate in a number of ways in activities involving the medical and biological sciences and stemming from the objectives and programs of both WHO and NIH. For example, limited funds have been made available to WHO for the support of projects of especial moment and of particular concern both to the United States and other countries. By way of illustration, the instance of support for an especial need in the field of atherosclerosis can be cited. In 1957, the National Advisory Heart Council recommended and the Surgeon General approved a grant to a WHO scientist to enable WHO to hold an international study-group meeting on the classification of atherosclerotic lesions, a significant step toward establishing international clarification and uniformity of information and terminology in this important field of disease.

More recently, a grant of $300,000 was made, from fiscal year 1958 funds, to WHO for the study of worldwide medical research needs and resources, a vitally needed study which should provide bases for the further planning, implementation, growth, and development of widely significant new activities on the part of all concerned with medical research and its advancement.

A second method of cooperation and working with WHO is one of principal interest and one which also further shows how international activities in the medical sciences can well be carried out through and within existing patterns of interchange and collaboration. This is consultation on research and related questions. WHO draws to a considerable extent on the PHS for such consultation; and among some 50 or more PHS staff who are currently serving or have served as WHO expert consultants on a wide variety of problems, there are 23 NIH staff members. Participating in expert advisory panels and committees established by WHO, these NIH scientists join with other scientists from all over the world selected by WHO on the basis of ability and technical experience. They are responsible for providing WHO with technical advice on a wide range of research and public health programs of international significance.

6. OTHER INTERNATIONAL NIH ACTIVITIES

Activities and relationships in the international medical research field not especially included in the preceding material involve principally three areas:

(*a*) There are several projects conducted under section 104K of Public Law 480 authorizing use of foreign currencies generated by the sale of United States agricultural surpluses overseas for such purposes as the translation of scientific material. These projects include one in India, two in Indonesia, and one in Poland. The projects involve the translation and abstracting of medical and related scientific literature, as in the fields of pharmacology; the development of a Chinese-English Medical Dictionary; and in the Polish project, translation of back volumes of selected Russian scientific journals in medical and biological fields.

(*b*) Although not an NIH responsibility, the Gorgas Memorial Laboratory in the Republic of Panama is financed through the NIH budget, $150,000 for this purpose being in fiscal year 1958 funds. The Laboratory, in Panama City, Panama, is the operating research establishment of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., a private, domestic, nonprofit corporation. An Act of Congress in 1928 authorized an annual contribution to support this activity. The Department of Health, Education, and Welfare through NIH serves solely as an administrative channel by which the Federal contribution can be requested of Congress and made available to the Laboratory. The Laboratory has carried on tropical diseases studies since 1929 and has made notable contributions to medical knowledge.

(*c*) NIH participates in the Interdepartmental Committee on Nutrition for National Defense, whose activities have profound international implications and whose research work is resulting in significant benefits for the free world.

Organized in 1954, the Committee includes representatives of the International Cooperation Administratiton and the Departments of State; Defense; Agriculture; and Health, Education, and Welfare. The Committee operates administratively through the National Institute of Arthritis and Metabolic Diseases. It is responsible for reviewing and coordinating nutrition projects being conducted by United States military and technical missions overseas where this country is providing assistance. It also provides technical advice and makes recommendations on ways of improving the nutrition of people in those areas.

Through this Committee the United States launched and continues a new kind of technical assistance program. Teams of specialists from NIH, the United States Army, universities, and other United States research centers have conducted surveys, trained counterpart personnel, provided advice and recommendations, and assisted in establishing nutrition programs in a number of areas. Since January, 1956, on request of the governments concerned, surveys have been completed in Iran, Pakistan, Korea, the Philippines, Turkey, and Libya. These have defined the major nutritional problems in these countries and established bases for developing nutrition services for their armed forces.

Several of these studies resulted directly from a nutrition conference held in Teheran, Iran, November, 1956, at the invitation of the Iranian government. Nutrition problems of mutual interest were discussed, along with plans for improving the nutritional status of people in the Near and Middle East. Plans were developed for the establishment of a Joint Intercountry Committee on Nutrition.

Other studies are underway or planned through the Interdepartmental Committee on the request of foreign governments, and each so far undertaken has been well-received and has produced results aiding materially in progress toward better health. The importance of this work is underlined by the fact that in most of the areas of the surveys, the primary concern of an estimated 90 percent of the people is survival, dependent upon food and shelter.

7. THE NATIONAL HEART INSTITUTE AND INTERNATIONAL RESEARCH

The National Heart Institute has shared in many of the activities of the National Institutes of Health in international aspects of medical research.

Interchange of scientific personnel. Thirty-eight visiting scientists and 57 guest workers have come to Heart Institute laboratories since the start of the Visiting Scientist and Guest Worker Programs. Seventy-two scientists from the National Heart Institute have studied abroad under the Research Fellowship Program and three foreign scientists are coming to the National Heart Institute under the new Postdoctoral Research Fellowship Program.

International Scientific Assemblies. The First, Second, and Third World Congresses of Cardiology have received partial support from the National Heart Institute. Several other international conferences of primary significance in cardiovascular research have received support. Among these are the International Blood Transfusion Congress, International Congress of Human Genetics, International Congress of Gerontology, International Symposium on Enzymes, International Committee on Nomenclature of Blood Clotting Factors, and the International Congress of Biochemistry.

In addition to making grants for travel, presentation of papers, planning, or other expenses of international meetings, the National Heart Institute helps in travel expenses for meetings as part of its support of grantees and of scientists working within the Institute itself.

International Research Activities. The National Heart Institute has made about 50 grants to research projects in other countries. Thirteen countries have been represented so far in the foreign grants area, and $742,387 has been expended.

Exchange Missions. The Ministry of Health of the Soviet Union in 1956 invited Dr. Paul Dudley White and other leading figures in the field of heart research and public health to visit centers for study and treatment of heart disease in the Soviet Union. Dr. James Watt, Director of the National Heart Institute, was a member of the mission. In 1957, leading Russian cardiologists made a reciprocal visit to the Heart Institute and other centers of heart research in the United States.

Cooperation with World Health Organization. One of the most important examples of cooperation between the research arm of the Public Health Service and the World Health Organization is the support given by the National Heart Institute to WHO for the International Meeting on Classification of Atherosclerotic Lesions. This meeting, held in 1957, has already stimulated research projects on atherosclerotic lesions in other countries.

Summary of NIH participation in international research, training, and other scientific activities by program area, fiscal year 1958

Program or activity	Number of grants or awards	Estimated obligations, fiscal year 1958
All programs, total	593	$3,619,671
1. International research activities, total	98	1,627,142
Research grants to foreign nationals (including cancer field investigations)	96	1,443,142
Cancer chemotherapy contract	1	60,000
Direct research activities outside the United States, Middle American Research Laboratory	1	124,000
2. Interchange of scientific personnel, total	225	1,247,620
Research fellowships, total	103	542,894
United States citizens outside United States	86	452,097
Fellows in United States from other countries	17	90,797
Training	1	17,152
Traineeships	21	153,574
Visiting scientists on duty at NIH	100	534,000
3. Interchange of scientific information, total	9	209,000
Russian translation program	9	209,000
(Grants to Excerpta Medica for abstracting) [1]	(3)	(50,945)
4. International scientific assemblies, total	260	235,909
Direct support of international meetings through grants to sponsoring organizations	10	85,909
Funds provided in research grants for attendance of grantees at international meetings	150	100,000
Travel to international meetings by NIH scientists	[2] 100	[2] 50,000
5. Cooperation with World Health Organization	1	300,000
Grant to WHO for study of worldwide medical research needs and resources	1	300,000

[1] Included in research grants to foreign nationals.
[2] Estimated.

Summary of NIH participation in international research, training, and other scientific activities by country, fiscal year 1958

Country	Total		Research projects		Fellowships		Traineeships		Foreign fellows in United States	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount
Total	221	$2,156,762	96	$1,443,142	86	$452,097	22	$170,726	17	$90,797
1. Argentina	5	40,290	4	30,030			1	10,260		
2. Australia										
3. Austria	2	10,883							2	10,883
4. Belgium	4	30,816	1	15,000	2	10,979			1	4,837
5. Brazil	1	25,975	1	25,975						
6. British Isles (United Kingdom)	73	607,414	6	232,035	54	295,924	11	69,820	2	9,635
7. Canada	27	300,256	19	245,341	5	22,263	[1] 3	32,652		
8. Chile	3	7,650	3	7,650						
9. Columbia	1	1,840	1	1,840						
10. Denmark	7	47,512	3	27,297	3	14,989			1	5,226
11. Eire	1	19,078	1	19,078						
12. Finland	5	50,972	4	45,180					1	5,792
13. France	9	72,727	3	45,776	4	17,519			2	9,432
14. Germany	8	42,699	1	10,000	5	22,786	1	5,600	1	4,313
15. Guatemala	2	60,709	2	60,709						
16. India										
17. Israel	10	102,999	8	96,698	2	6,301				
18. Italy	4	34,365	2	20,350	1	8,000			1	6,015
19. Japan	6	61,700	6	61,700						
20. Lebanon	4	37,273	4	37,273						
21. Liberia	1	23,958	1	23,958						
22. Mexico	3	24,650	3	24,650						
23. Netherlands	9	139,859	[2] 7	128,762	1	5,684			1	5,413
24. New Zealand	1	4,200	1	4,200						
25. Norway	3	25,132	1	14,875					2	10,257
26. Panama	2	76,385	2	76,385						
27. Peru	2	25,050	2	25,050						
28. Philippines	1	18,100	1	18,100						
29. South Africa	3	52,371	3	52,371						
30. Sweden	17	168,033	5	87,600	6	35,794	4	31,740	2	12,899
31. Switzerland	7	43,866	1	5,259			2	20,654	1	6,095

[1] Includes 1 training grant amounting to $17,152.
[2] Includes 3 cancer field investigation projects totaling $71,817.

GLOSSARY OF ABBREVIATIONS USED IN THE FOLLOWING LISTS

Letters that prefix the grant number identify the supporting institute or division.

A	National Institute of Arthritis and Metabolic Diseases.
B	National Institute of Neurological Diseases and Blindness.
C	National Cancer Institute.
D	National Institute of Dental Research.
E	National Institute of Allergy and Infectious Diseases.
G	Division of Research Grants.
H	National Heart Institute.
M	National Institute of Mental Health.

The following symbols are used to identify the type of fellowship:

(F)	Postdoctoral fellows from other countries.
(PD)	Postdoctoral.
(PM)	Predoctoral.
(PS)	Postsophomore.
(PT)	Part-time.
(SP)	Special.
(SR)	Senior.

The following abbreviations are used to identify study sections:

A&I	Allergy & Infectious Diseases.
ACEB	Advisory Committee on Epidemiology & Biometry.
BBC	Biophysics & Biophysical Chemistry.
Bio	Biochemistry.
B&M	Bacteriology & Mycology.
BS	Behavioral Sciences.
Cardio	Cardiovascular.
CB	Cell Biology.
Cy	Cancer Chemotherapy.
Dental	Dental.
Endo	Endocrinology.
Gen	Genetics.
GM	General Medicine.
HCETGC	Health Council Experimental Training Grants Committee.
HED	Human Embryology & Development.
Hema	Hematology.
HFR	Hospital Facilities Research.
Micro	Microbiology.
M&G	Morphology & Genetics.
MH	Mental Health.
MHPG	Mental Health Project Grants Program.
MHSC	Mental Health Selection Committee.
MHSGRC	Mental Health Small Grants Review Committee.
M&N	Metabolism & Nutrition.
My	Mental Health Psychopharmacology.
Neuro	Neurology.
NFIC	Neurology Field Investigations Committee.
NR	Nursing Research.
Path	Pathology.
PET	Pharmacology & Experimental Therapeutics.
PHR	Public Health Research.
Physio	Physiology.
PTM	Parasitology & Tropical Medicine.
Rad	Radiation.
SD	Sensory Diseases.
SEOH	Sanitary Engineering & Occupational Health.
SSS	Special Study Section.
SSSMD	Special Study Section Multidisciplinary.
Surg	Surgery.
V&R	Virology & Rickettsiology.

Research grants to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958

Country, city, institution, and investigator	Project title	Grant No.	Study section	Amount
ARGENTINA				
Buenos Aires:				
Instituto de Biologia y Medicina Experimental: Houssay, B. A. Institution total, 1 grant, $2,500.	Experimental diabetes	A-18C8	Endo	$2,500
Instituto de Investigaciones Bioquemicas, Campomar Foundacion: Leloir, L. F. Institution total, 1 grant, $12,200.	Enzymes and coenzymes acting on hexosephosphates.	G-3442C6	Bio	12,200
Ramos Mejia Hospital: Cabrini, R. L. Institution total, 1 grant, $530.	Mast cells in oral and nasal mucosae.	H-3575	M&G	530
University of Buenos Aires; De Robertis, E. Institution total, 1 grant, $14,800.	Ultrastructure of synaptic endings.	B-1549	Path	14,800
National total, 4 grants				30,030
BELGIUM				
Ghent: University of Ghent: Heymans, C. Institution total, 1 grant, $15,000.	Basoceptors in hypertension, hypothermia, lung.	H-3393	Cardio	15,000
National total, 1 grant				15,000
BRAZIL				
Rio de Janeiro: University of Brazil: Chagas, C. Institution total, 1 grant, $25,975.	Study of the mechanism of curarization.	B-1471	PET	25,975
National total, 1 grant				25,975
BRITISH ISLES				
London:				
Chester Beatty Research Institution: Haddow, A. Institution total, 1 grant, $150,000.	Cancer chemotherapy	C-3188C1	Cy	150,000
Medical Research Council of Great Britain and Ireland: King, A. J. Institution total, 1 grant, $25,000.	Nonspecific genital infection	E-652C2	Micro	25,000
University of London:				
Elek, S. D	Serology of human and rat leprosy bacilli.	E-1899	A & I	4,000
Franklin, R. Institution total, 2 grants, $32,345.	Molecular structure of viruses	E-1772	BBC	28,345
Oxford: University of Oxford: Krebs, H. A. Institution total, 1 grant, $12,040.	Fine structure and enzymology of bacterial organelles.	C-3929	BBC	12,040
Reading: University of Reading: Ditchburn, R. W. Institution total, 1 grant, $12,650.	Eye movements in relation to visual perception.	B-1233C1	SD	12,650
National total, 6 grants				232,035
CANADA				
Halifax: Dalhousie University: Godden, J. O. Institution total, 1 grant, $10,450.	Epidemiologic survey of selected neurological disorders.	B-9059	NFIC	10,450
Kingston: Queen's University: West, A. S. Institution total, 1 grant, $9,200.	Reactions to insect bites: causes and effects.	E-1155C1	PTM	9,200

Research grants to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958—Continued

Country, city, institution, and investigator	Project title	Grant No.	Study section	Amount
CANADA—continued				
Montreal: McGill University:				
Cleghorn, R. A	Psychodynamic changes with pharmacotherapy.	M-1794	My	$13,225
Fairbairn, D	Biochemistry and physiology of *Ascaris lumbricoides*.	E-2138	PTM	13,174
Fraser, F. C	Genetics of arthrogryposis multiplex congenita.	A-1959	M & G	2,300
Do	Genetics of the epilepsies	B-706C3	M & G	13,190
Leblond, C. P	Influence of aging on various cell populations.	H-3783	M & G	15,785
Malmo, R. B	Specificity of physiological reactions to stress.	M-1475C1	MH	16,675
Quastel, J. H	Absorption of carcinogens by intestine.	C-3596	Physio	9,072
Rose, B	Hypersensitivity mechanisms in man.	E-1322C1	SSS	17,000
Venning, E. H	Mechanisms in the secretion of aldosterone.	H-2716C1	Endo	9,600
Wittkower, E. D	Psychopharmacology of psychosomatic skin disorders.	M-2151	My	17,250
Institution total, 10 grants, $127,271.				
University of Montreal: Selye, H.	The mechanism of acute infarctoid cardiopathy.	H-3688	SSS	8,640
Institution total, 1 grant, $8,640.				
Toronto: University of Toronto: Graham, A. F	Study of host virus relationship	E-262C6	M&G	19,895
Nikiforuk, G	Carbohydrate components in teeth.	D-594C1	Dental	7,350
Institution total, 2 grants, $27,245.				
Vancouver: University of British Columbia: Khorana, H. G	Chemical and enzymatic studies of polynucleotides.	C-3106C1	Bio	13,200
Do	do	C-3106C1S1	Bio	17,075
Patterson, J. W	Experimental cataracts	A-1831	SD	21,735
Institution total, 3 grants, $52,010.				
Winnipeg: University of Manitoba: Chown, B.	Materno-fetal barrier and Rh	H-3238	HED	10,525
Institution total, 1 grant, $10,525.				
National total, 19 grants				245,341
CHILE				
Santiago: Chile University School of Medicine: Agosin, M	Metabolism of *Echinococcus granulosus*.	E-1867	PTM	3,150
Cori, O	Biosynthesis of phosphocreatine and phosphoarginine.	G-5631	Bio	2,300
Rotman, B	Beta-galactosidase enzyme activity in *E. coli*.	E-2019	Micro	2,200
Institution total, 3 grants, $7,650.				
National total, 3 grants				7,650
COLOMBIA				
Bogota: Hospital de San Juan de Dios: Lichtenberger, E.	Study on atherosclerosis in Colombia.	H-3705	Path	1,840
Institution total, 1 grant, $1,840.				
National total, 1 grant				1,840

Research grants to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958—Continued

Country, city, institution, and investigator	Project title	Grant No.	Study section	Amount
DENMARK				
Copenhagen:				
Danish Cancer Registry: Clemmesen, J.	Endemiology of cancer in Denmark.	C-3087C1	Path	$6,180
Institution total, 1 grant, $6,180.				
State Serum Institute: Slim, J. C.	Studies on acquired toxoplasmosis.	E-1741	PTM	12,515
Institution total, 1 grant, $12,515.				
University of Copenhagen: Kemp, T.	Heredity in certain types of cancer.	C-948C9	M&G	8,602
Institution total, 1 grant, $8,602.				
National total, 3 grants				27,297
EIRE				
Dublin: St. Kevin's Hospitals: Harman, J. W.	Structural stability of erythrocytes in anemias.	H-3276	Hema	19,078
Institution total, 1 grant, $19,078.				
National total, 1 grant				19,078
FINLAND				
Helsinki: University of Helsinki:				
Eranko, E. O	Function of adrenal medulla	A-1725	Endo	17,060
Setala, K	Mechanism of carcinogenesis in mice and rabbits.	C-2930C1	M&G	5,000
Do	do	C-2930C1S1	M&G	15,120
von Bonsdorff, B	Vitamin B_{12} deficiency in tape worm infestation.	E-1693	PTM	8,000
Institution total, 4 grants, $45,180.				
National total, 4 grants				45,180
FRANCE				
Paris:				
Pasteur Institut:				
Lacassagne, A	Mechanism of carcinogenesis by conjugated molecules.	C-524C10	SSS	15,566
Moser, C. M	Theoretical investigations on carcinogenic activity.	C-3065C1	BBC	25,300
Institution total, 2 grants, $40,866.				
University of Paris: Pullman, B.	Electronic molecular structure and cancer chemotherapy.	C-3073C1	BBC	4,910
Institution total, 1 grant, $4,910.				
National total, 3 grants				45,776
GERMANY				
Heidelberg: University of Heidelberg: Lettre, H.	Chemotherapeutic effect of tumor cell components.	C-2735R1	Cy	10,000
Institution total, 1 grant, $10,000.				
National total, 1 grant				10,000
GUATEMALA				
Guatemala City: Pan American Sanitary Bureau:				
Scrimshaw, N. S	Dietary factors in kwashiorkor	A-981C2	M&N	27,750
Do	Comparative epidemiology of atherosclerosis.	H-2653C1	PHR	32,959
Institution total, 2 grants, $60,709.				
National total, 2 grants.				60,709

Research grants to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958—Continued

Country, city, institution, and investigator	Project title	Grant No.	Study section	Amount
ISRAEL				
Jerusalem: Hebrew University:				
Bergmann, E. D	Aliphatic fluoro-compounds	C-3095C1	Cy	$16,330
Feldman-Muehsam, B	Bionomics of ticks	E-1006C2	PTM	4,715
Hestrin, S	Synthesis of cellulose and related polysaccharides.	E-1494C1	Bio	10,000
Theodor, O	Parasites of wild mammals and birds.	E-1315C1	PTM	2,100
Institution total, 4 grants, $33,145.				
Rehovoth: Weizmann Institute of Science:				
Katchalski, E	Water-soluble poly- and amino acids.	H-2279C1	BBC	20,000
Do	do	H-2279C1S1	BBC	21,600
Lavie, D	Antitumor compounds from *Ecballium* and related plants.	C-2810C2	Cy	10,963
Sondheimer, F	Synthesis of the cardiac-active steroidal lactones.	H-2476C1	PET	11,000
Institutional total, 4 grants, $63,553.				
National total, 8 grants				96,698
ITALY				
Naples: Anton and Reinhard Dohrn Foundation:				
Dohrn, P	Cell growth, division, metabolism and related problems.	C-3402C1	SSS	10,000
Ghiretti, F	Metallo-proteins in marine invertebrates.	G-4845C1	Bio	10,350
Institution total, 2 grants, $20,350.				
National total, 2 grants				20,350
JAPAN				
Kitaku: Osaka University Medical School: Miyaji, T	Hepatoma and cirrhosis in Japan	C-3481	Path	5,500
Institution total, 1 grant, $5,500.				
Kofu City: Yamanashi Medical Research Institute: Sugiura, S	Biological studies of *Schistosoma japonicum*.	E-1109C1	PTM	5,750
Institution total, 1 grant, $5,750.				
Kyoto: Kyoto University, Hayashi, O.	Studies on oxygenases	C-4222	Bio	17,000
Institution total, 1 grant, $17,000.				
Tokyo:				
Japanese Association of Medical Sciences: Okinaka, S.	Epidemiologic survey of selected neurologic disorders.	B-9065	NFIC	20,690
Institution total, 1 grant, $20,690.				
Medical Institute of Sasaki Foundation:				
Yoshida, T	Ascites tumor system for chemotherapy screening.	C-2799C2	Cy	7,200
Do	do	C-2799C2S1	Cy	5,560
Institution total, 2 grants, $12,760.				
National total, 6 grants.				61,700

Research grants to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958—Continued

Country, city, institution, and investigator	Project title	Grant No.	Study section	Amount
LEBANON				
Beirut: American University of Beirut:				
Harris, R. C	Study of liver disease in infants and children.	A-2678	GM	$5,387
Schwabe, C. W	Host-parasite relationships in echinococcosis.	E-2205	PTM	20,095
Scott, V. C	Adrenal function and antidiuretic hormone.	G-5172	HED	6,645
Shanklin, W. M	A histological study of neurosecretion in man.	B-1701	M&G	5,146
Institution total, 4 grants, $37,273.				
National total, 4 grants				37,273
LIBERIA				
Harbel: Liberian Institute of Tropical Medicine, Inc.: Miller, M. J.	Epidemiology of *Plasmodium malariae*.	E-1022C2	PTM	23,958
Institution total, 1 grant, $23,958.				
National total, 1 grant				23,958
MEXICO				
Mexico, D. F.:				
General Hospital: Solanes, M. P.	Intraocular pressure in Indians, mestizos and whites.	B-1326C1	SD	8,000
Institution total, 1 grant, $8,000.				
Hospital Infantil: Gomez, S. F.	Infantile protein malnutrition	A-1520	M&N	15,000
Institution total, 1 grant, $15,000.				
University of Mexico: Villa-Ramirez, B.	Role of bats in transmission of rabies.	E-2001	PTM	1,650
Institution total, 1 grant, $1,650.				
National total, 3 grants				24,650
NETHERLANDS				
Amsterdam:				
Excerpta Medica Foundation: Woerdeman, M. W.	Publication of Cardiovascular Abstracting Journal.	H-2898C1	SSS	23,000
Do	Publication of Gerontology Abstracting Journal.	H-3621	SSS	13,973
Do	do	M-2373	SSS	13,972
Institution total, 3 grants, $50,945.				
Netherlands Cancer Institute: Muhlbock, O.	Hormonal genesis of mammary cancer.	C-3431	M&G	6,000
Institution total, 1 grant, $6,000.				
National total, 4 grants				56,945
NEW ZEALAND				
Christchurch: North Canterbury Hospital Board: Gunz, F. W.	Incidence and etiology of leukemia in New Zealand.	C-3707	Hema	4,20
Institution total, 1 grant, $4,200.				
National total, 1 grant				4,200

Research grants to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958—Continued

Country, city, institution, and investigator	Project title	Grant No.	Study section	Amount
NORWAY				
Oslo: Oslo University: Skard, A. G.	Children's personality development.	M-1737R1	MH	$14,875
Institution total, 1 grant, $14,875.				
National total, 1 grant				14,875
PANAMA				
Panama: Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc.:				
Hertig, M	Transmission of leishmaniasis in Panama.	E-1251C1	PTM	43,840
Johnson, C. M	Ecology of sylvan yellow fever in Panama.	E-1941	PTM	32,545
Institution total, 2 grants, $76,385.				
National total, 2 grants				76,385
PERU				
Lima: Universidad Nacional Mayor de San Marcos: Hurtado, A	Therapy of *Pseudomonas* infections.	G-3123C6S1	Surg	2,637
Do	do	G-3123C7	Surg	22,413
Institution total, 2 grants, $25,050.				
National total, 2 grants.				25,050
PHILIPPINES				
Manila: University of the Philippines: Camara, A. A.	Edema in beriberi and other deficiency states.	H-1720C3	M&N	18,100
Institution total, 1 grant, $18,100.				
National total, 1 grant				18,100
SOUTH AFRICA				
Cape Town: University of Cape Town: Brock, J. F.	Dietary fat, serum cholesterol and heart disease.	H-3316	M&N	10,000
Institution total, 1 grant, $10,000.				
Durban: South African Council for Scientific and Industrial Research:				
Elsdondew, R	Factors determining invasiveness in *E. histolytica*.	E-1592S1	PTM	17,388
Do	do	E-1592C1	PTM	24,983
Institution total, 2 grants, $42,371.				
National total, 3 grants.				52,371
SWEDEN				
Lund: University of Lund: Bergstrom, S	Metabolism of steroids and bile acids.	H-2842C1	M&N	15,000
Gustafsson, B. E	Rearing of a colony of germ-free rats.	A-1933	M&N	15,000
Institution total, 2 grants, $30,000.				

Research grants to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958—Continued

Country, city, institution, and investigator	Project title	Grant No.	Study section	Amount
SWEDEN—continued				
Stockholm: Karolinska Institutet:				
Capersson, T.	Quantitative cytochemical studies of the cell.	C-3082C1	BBC	$30,000
Engstrom, A.	Biophysical studies of bone and teeth.	D-700	BBC	12,600
Klein, G.	Cytogenetics of variability in cancer cell populations.	C-3700	M&G	15,000
Institution total, 3 grants, $57,600.				
National total, 5 grants				87,600
SWITZERLAND				
Lausanne: Institut D'Anatomie Pathologique: Rabinowicz, T. Institution total, 1 grant, $5,259.	Prenatal development of the human cerebral cortex.	M-1561	Path	5,259
National total, 1 grant				5,259

Research fellowships to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958

Name of fellow	Type	Department, laboratory, or students	Sponsor or director	Inst./div.
BELGIUM				
Brussels: University of Brussels: Perry, R. P.	PD	Cytology	Brachet, J.	C
Louvain: University of Louvain: Sellinger, O. Z.	PD	Physical chemistry	De Duve, C.	C
BRITISH ISLES				
Belfast: Queen's University: Meyers, M. B.	PD	Chemistry	Henbest, H. B.	H
Birmingham: Birmingham University: Reeves, T. J.	SP	Medicine	Arnott, W. M.	H
Cambridge:				
A. R. C. Institute of Animal Physiology: Dittmer, J. C.	PD	Biochemistry	Dawson, R. M. C.	H
Cambridge University:				
Battaglia, F. C.	PD	Biochemistry	Young, F. G.	G
Blank, M.	PD	Chemistry	Roughton, F. J. W.	H
Dunham, E. T.	SP	Physiology	Hodgkin, A. L.	H
Gross, D.	PD	Biochemistry	Sanger, F.	A
Harding, B. W.	PD	do	Samuels, L. T.	C
Hemingway, A.	SP	Physiology	Roughton, F. J. W.	H
Klopman, R. B.	PM	Zoology	Hinde, R. A.	M
Konugres, A. A.	PM	Pathology and pathobiology.	Coombs, R. R. A.	H
Looney, W. B.	SP	Physics	Mitchell, J. S.	G
McCollester, D.	PD	Biochemistry	Young, F. G.	H
Millich, F.	PD	Chemistry	Todd, A. R.	C
Moncure, H., Jr.	PD	do	Todd, A.	C
Murayama, M.	SP	do	Perutz, M.	C
Stempien, M. F.	PD	do	Todd, A. R.	C
Do	PD	do	do	C
Zeigler, H. P.	PD	Zoology	Thorpe, W. H.	M
Cavendish Laboratory: Stockell, A.	PD	Biochemistry	Perutz, M.	A
Edinburgh: Edinburgh University:				
Fennoy, L. V.	PD	Pharmacology and pharmacy.	Barlow, R. B.	B
Glassman, E.	PD	Genetics	Waddington, C. H.	C
Pace, M. G.	PD	Zoology	Mitchison, N. A.	C
Rustad, R. C.	PD	do	Swann, M. M.	C

Research fellowships to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958—Continued

Name of fellow	Type	Department, laboratory, or students	Sponsor or director	Inst./ div.
BRITISH ISLES—continued				
London:				
Chester Beatty Research Institute:				
Goodwin, P. N	PM	Physics	Mayneord, W. V	C
Kirkman, H	SP	Oncology	Haddow, A	C
Hospital For Sick Children:				
Jensen, P. J	PD	Hematology	Cathie, I. A. B	H
Mayer, F. E	PD	Cardiology	Bonham-Carter, R. E	H
Medical Research Council of Great Britain and Ireland: Amrein, Y. U.	SP	Chemotherapy	Fulton, J. D	E
Royal Institution of Great Britain: Lubrosky, S. W.	PD	Chemistry	Gutfreund, H	C
Royal Marsden Hospital: Morrow, J. W.	SP	Urology	Wallace, D. M	C
University College Hospital Medical School:				
Boyer, S. H	PD	Genetics	Penrose, L. S	H
Cosmos, E	PD	Biophysics	Katz, B	G
Gerald, P. S	SP	Genetics	Penrose, L	H
University of London:				
Bartsch, G. E	PD	Biostatistics	Hill, A. B	G
Beeson, P. B	SP	Microbiology	Cruickshank, R	E
Cleland, R. E	PD	Botany	Bennet-Clark, T. A	C
Duffy, B. J	SP	Physiology	Hill, B	C
Garcia, J. F	PD	Endocrinology	Harris, G. W	B
Iber, F. L	SP	Medicine	Sherlock, S	H
Levy, H. R	PD	Radiology	Ponjak, G	C
Moss, J. W	PD	Psychology	O'Connor, N	M
Munz, F. W	PD	Opthalmology	Dartnall, H. J. A	B
Ogden, T. E	PD	Physiology	Cobb, W. A	B
Potter, D. D	PD	Biophysics	Katz, B	B
Scheline, R. R	PD	Biochemistry	Williams, R. T	E
Shafter, H. A	PD	Cardiology	Leathan, A	H
Sjodin, R. A	PD	Biophysics	Harris, E. J	B
Middlesex: Mount Vernon Hospital: Gunther, R. L.	PD	Radiology	Gray, L. H	C
Oxford: University of Oxford:				
Grant, L. H	SP	Pathology and pathobiology.	Florey, H	H
MacMillan, W	SP	Pharmacology and pharmacy.	Burn, J	H
Remers, W. A	PD	Chemistry	Jones, E. R	E
Schaad, L. J	PD	Biostatistics	Coulson, C. A	C
Shipp, J. C	SP	Biochemistry	Krebs, H. A	A
CANADA				
Montreal: McGill University:				
Bovard, E. W	SP	Neurology	Jasper, H. H	M
Branch, C. L	PD	Physiology	do	B
Jane, J. A	PD	Neurology	do	M
Rayport, M	PD	do	do	B
Ottawa: Department of National Health and Welfare: Powelson, D. M.	SP	Hygiene and public health.	Morgan, J. F	C
DENMARK				
Copenrhagen:				
Calsberb Foundation: Frieden, E.	SP	Chemistry	Linderstrom-Lang, K	A
University of Copenhagen:				
Cooperstein, I	SP	Biology and biological sciences.	Ussing, H	H
Hanawalt, P. C	PD	Microbiology	Maaløe, O	C
FRANCE				
Paris: University of Paris:				
Bonner, B. A	PD	Genetics	Ephrussi, B	E
Dimick, D. F	PD	Biochemistry	Jayle, M.-F	C
Hawthorne, D. C	PD	Genetics	Ephrussi, B	C
Plante, L. T	PD	Radiology	Buu-Hoi, N. P	C

Research fellowships to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958—Continued

Name of fellow	Type	Department, laboratory, or students	Sponsor or director	Inst./ div.
GERMANY				
Buldern: Max Planck Institut Für Verhaltens Physiologie:				
Barlow, G. W.	PD	Physiology	Lorenz, K. Z.	M
Burchard, J. E., Jr.	PD	Biology and bilogical sciences.	do.	M
Kiel: University of Kiel: Ekberg, D. R.	PD	Zoology	Precht, H.	B
Munich: University of Munich: Jensen, E. V.	SP	Biochemistry	Butenandt, A.	C
Tubingen: Max-Planck Institut für Biologie: Wright, T. R.	PD	Genetics	Kuhn, A.	C
ISRAEL				
Rehoboth: Weismann Institute of Science:				
Krakower, G. W.	PD	Chemistry	Sondheimer, F.	H
Rosenthal, D. W.	PD	Organic chemistry	do.	C
ITALY				
Rome: Instituto Superiore di Sanita: Lewis, R. W.	SP	Microbiology	Chain, E. B.	G
NETHERLANDS				
Utrecht: University of Utrecht: Kelly, D. E.	PD	Histology	Van de Kamer, J. C.	B
SWEDEN				
Lund: University of Lund:				
Glasky, A. J.	PD	Biochemistry	Ehrensvard, G.	C
Jordan, P. H., Jr.	SP	do.	Bergstrom, S.	H
Nikitovitch-Winer, M.	PD	Endocrinology	Jacobsohn, D.	A
Stockholm:				
Karolinska Institutet: Winer, A. D.	PD	Biochemistry	Theorell, H.	B
Stockholm Hospitals: Cota-Robles, E.	PD	Chemistry	Weibull, C.	E
University of Stockholm: Morgan, W. S.	SP	Biochemistry	Multin, T.	C
SWITZERLAND				
Bern: University of Bern: Kahn, J.B.Jr.	SP	Pharmacology and pharmacy.	Wilbrandt, W.	H
Geneva: University of Geneva: Franklin, N. C.	PD	Biophysics	Kellenberger, E.	C
Zurich: Swiss Federal Institute of Technology: Smith, H. E.	PD	Chemistry	Prelog, V.	A

Field investigation grants to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958

Investigator	Project	Grant	Amount
NETHERLANDS			
Amsterdam: Excerpta Medica Foundation: Woerdeman, M. W.	Continuation of the cancer section	C-9346C4	$5,162
	Translations and publication "Abstract of Soviet Medicine.	C-9506C1	49,000
	Translations "Onkologiia"	C-9558	17,655
Institutional total, 3 grants, $71,817.			
National total, 3 grants			71,817

Training grants to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958

Director	Grant No.	Amount
CANADA		
Montreal: McGill University: McNoughton, F. L.	B-5161C1	$17,152
Institution total, 1 grant, $17,152.		
National total, 1 grant		17,152

Traineeships to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958

Trainee	Award No.	Amount
ARGENTINA		
Buenos Aires: Instituto de Investigaciones Bioquemicas, Campomar Foundation: Pogell, B. M.	B-337	$10,260
Institution total, 1 award, $10,260.		
National total, 1 award		10,260
BRITISH ISLES		
Cambridge: Cambridge University:		
Botelho, S. Y.	B-327	8,900
Moulton, J.	B-335	9,000
Institution total, 2 awards, $17,900.		
London:		
Kings College: Ryan, J. C.	B-406	6,000
Institution total, 1 award, $6,000.		
University College Hospital Medical School: Sjodin, R. A.	B-403	6,200
Institution total, 1 award, $6,200.		
University of London:		
Bogdanove, E.	B-368	8,400
Federman, D. C.	A-313E1	3,976
Jarcho, L.	B-294	11,416
Reinmuth, O. M.	B-261S1	2,000
Shipley, T.	B-436	7,410
Westerman, M.	A-267E1	850
Institution total, 6 awards, $34,052.		
Taplow: Medical Research Council Canadian Red Cross Memorial Hospital: Baum, J.	A-276C1	5,668
Institution total, 1 award, $5,668.		
National total, 11 awards		69,820
CANADA		
Montreal: McGill University:		
Barber, J. B.	B-371	8,500
Rovit, R. L.	B-173C1	7,000
Institution total, 2 awards, $15,500.		
National total, 2 awards		15,500
GERMANY		
Dusseldorf: Medical Academy: Hickman, L. W.	H-763C1	5,600
Institution total, 1 award, $5,600.		
National total, 1 award		5,600
SWEDEN		
Gothenburg: University of Gothenburg: Paly, S. N.	B-352	7,250
Institution total, 1 award, $7,250.		
Stockholm:		
Karolinska Institutet: Smith, C.	B-425	6,500
Institution total, 1 award, $6,500.		
Serafimerlasarettet:		
Galloway, J. R.	B-355	8,240
Ring, B. A.	B-331	9,750
Institution total, 2 awards, $17,990.		
National total, 4 awards		31,740

Traineeships to scientists of foreign countries awarded from appropriations to NIH for fiscal year 1958—Continued

Trainee	Award No.	Amount
SWITZERLAND		
Bern: University of Bern: Moses, R. A	B-342	12,000
Institution total, 1 award, $12,000.		
Lausanne: University of Lausanne: Steinberg, M	H-864	8,654
Institution total, 1 award, $8,654.		
National total, 2 awards		20,654

Postdoctoral research fellowships for foreign scientists: Awardees selected (Foreign Fellows in the United States)

Name and number	Country	Home address	Field	Sponsor and institution
Preining, Othmar FF-28	Austria	Wien 9, Praterstabe 36/28, Austria	Physics	Dr. S. Goetz, California Institute of Technology, Pasadena, Calif.
Holzner, Johann H FF-29	do	17 Rienossigasse, Vienna 4, Austria	Histochemistry	Dr. Hans Popper, Mount Sinai Hospital, New York City, N. Y.
Dumont, Jacques Emile FF-16	Belgium	25a, Ave. de l'Oree, Ixelles-Bruxelles, Belgium.	Endocrinology	Dr. J. B. Stanbury, Massachusetts General Hospital, Boston, Mass.
Killmann, Sven-Aage FF-22 (withdrew June 30, 1958)	Denmark	5, Hornstrupvej, Copenhagen, Vanløse, Denmark.	Hematology	Dr. E. P. Kronkite, Brookhaven National Laboratory, Upton, Long Island, N. Y.
Vilkki, Panu Ilmari FF-19	Finland	Betaniankatu 1. C., 20 Turku, Finland	Biochemistry	Dr. J. E. Rall, NIAMD, NIH, Bethesda, Md.
Laroche, Marie-Jeanne FF-2	France	6 Rue de Beaute, Nogent-sur-Marne, Seine, France.	Pharmacodynamy	Dr. B. B. Brodie, NHI, NIH, Bethesda, Md.
Tanzer, Joseph FF-4	do	48 rue Compans, Paris 19 e, France	Hematology	Dr. E. E. Osgood, University of Oregon Medical School, Portland, Oreg.
Dengler, Hans Josef FF-25	Germany	Heidelberg, Medizinische, Universitatsklinik, Germany (Western Zone).	Biochemistry	Dr. B. B. Brodie, NHI, NIH, Bethesda, Md.
Cross, Kenneth William FF-38	Great Britain	5 Summerfield Rd., London W. 5, England	Respiratory physiology	Dr. J. R. Comroe, Jr., Cardiovascular Research Institute, University of California Medical Centre.
Doig, Andrew FF-35	do	22 Dublin St., Edinburgh 3, Scotland	Gastroenterology and renal disorders.	Dr. Robert M. Kark, Department of Medicine, University of Illinois.
Vos, Otto FF-40	Holland	Anna van Buerenstraat 28, Leiderdorp	Radiology	Dr. A. Hollaender, Oak Ridge National Laboratory, Oak Ridge, Tenn.
Agostoni, Emilio FF-31	Italy	78/1 Corso di Porto Romano, Milano, Italy	Physiology	Dr. Wallace O. Fenn, University of Rochester, School of Medicine and Dentistry, Rochester, N. Y.
Bremer, Jon FF-42	Norway	Vollebekk	Physiological chemistry	Dr. David M. Greenberg, University of California, Berkeley, Calif.
Foss, Olav Per FF-14	do	Det Norske, Radium Hospital, Oslo, Norway.	Clinical laboratory, technology.	Dr. D. D. Van Slyke, Brookhaven National Laboratory, Upton, Long Island, N. Y.
Linderholm, P. Hakan G FF-7	Sweden	Klin. fysiol. lab., Karolinska sjukhuset, Stockholm 60, Sweden.	Clinical physiology	Dr. A. B. DuBois, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa.
deVerdier, Carl-Henric FF-5	do	Institute of Medical Chemistry, University of Uppsala, Sweden.	Biochemistry	Dr. Van Potter, Laboratory for Cancer Research, University of Wisconsin Medical School, Madison, Wis.
de Weck, Alain L FF-12	Switzerland	5, Ave. Hentsch, Geneva, Switzerland	Dermatology (allergy)	Dr. H. E. Eisen, Washington University School of Medicine, St. Louis, Mo.

MAJOR EVENTS IN NIH HISTORY

PUBLIC HEALTH SERVICE SPEARHEADS
NEW ERA IN MEDICAL RESEARCH

1887
RESEARCH LABORATORY FOUNDED AT STATEN ISLAND, N.Y.

1930
HYGIENIC LABORATORY BECOMES NIH

1937
CONGRESS AUTHORIZES NATIONAL CANCER INSTITUTE

1938
NIH MOVES TO BETHESDA, MD.

1947–58

1947 Division of Research Grants

1948 National Heart Institute
National Institute of Dental Research
National Institute of Allergy and Infectious Diseases

1949 National Institute of Mental Health

1950 National Institute of Arthritis and Metabolic Diseases
National Institute of Neurological Diseases and Blindness

1953 Department of Health, Education, and Welfare
Clinical Center

1955 Division of Biologics Standards
Division of Research Services
Division of Business Operations

1958 Division of General Medical Sciences

INTERNATIONAL ACTIVITIES OF NIH

WORLD-WIDE COOPERATION IS ESSENTIAL TO MODERN MEDICAL RESEARCH

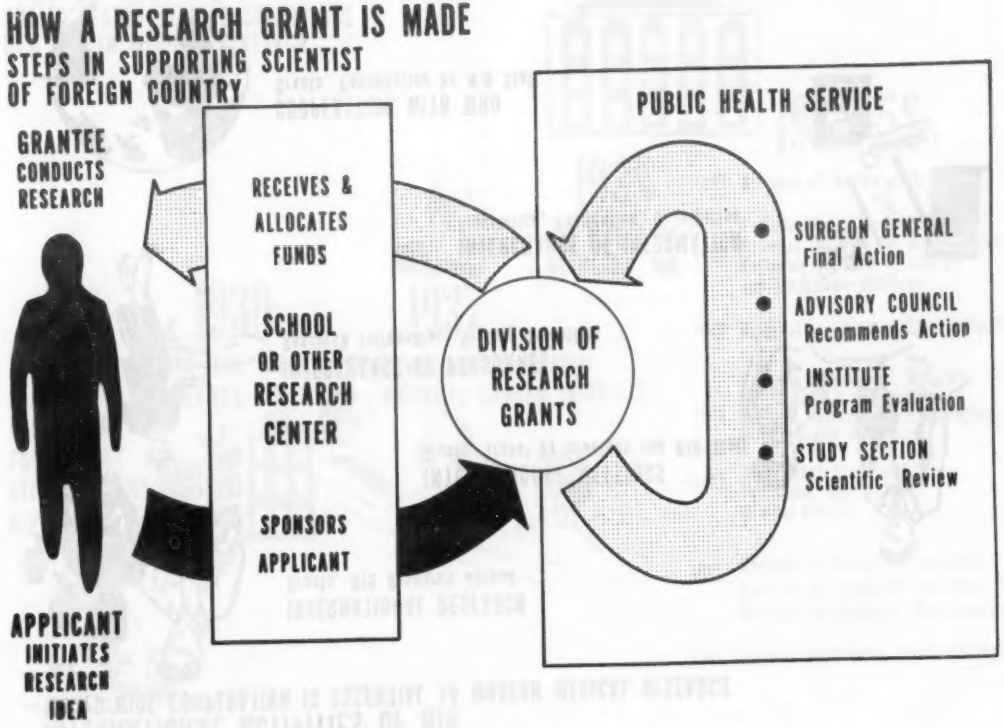
INTERNATIONAL RESEARCH
Grants, NIH Research Abroad

INTERNATIONAL MEETINGS
Grants, Travel by Grantees and NIH Staff

INTERCHANGE OF PERSONNEL
Research Fellowships, Visiting Scientists

INTERCHANGE OF INFORMATION
Translation, Publication, Distribution

COOPERATION WITH WHO
Grants, Consultation by NIH Staff


HOW A RESEARCH GRANT IS MADE
STEPS IN SUPPORTING SCIENTIST OF FOREIGN COUNTRY
GRANTEE CONDUCTS RESEARCH
APPLICANT INITIATES RESEARCH IDEA
RECEIVES & ALLOCATES FUNDS
SCHOOL OR OTHER RESEARCH CENTER
SPONSORS APPLICANT
DIVISION OF RESEARCH GRANTS
PUBLIC HEALTH SERVICE
SURGEON GENERAL Final Action
ADVISORY COUNCIL Recommends Action
INSTITUTE Program Evaluation
STUDY SECTION Scientific Review

TEAMWORK IN MEDICAL RESEARCH

TYPICAL COORDINATED STAGES IN RESEARCH PROGRESS

First Stage
TEST TUBE

Most medical advances today grow out of fundamental laboratory research conducted largely with pencil and crude materials. Biology, organic chemistry, and biophysics predominate

Second Stage
ANIMAL

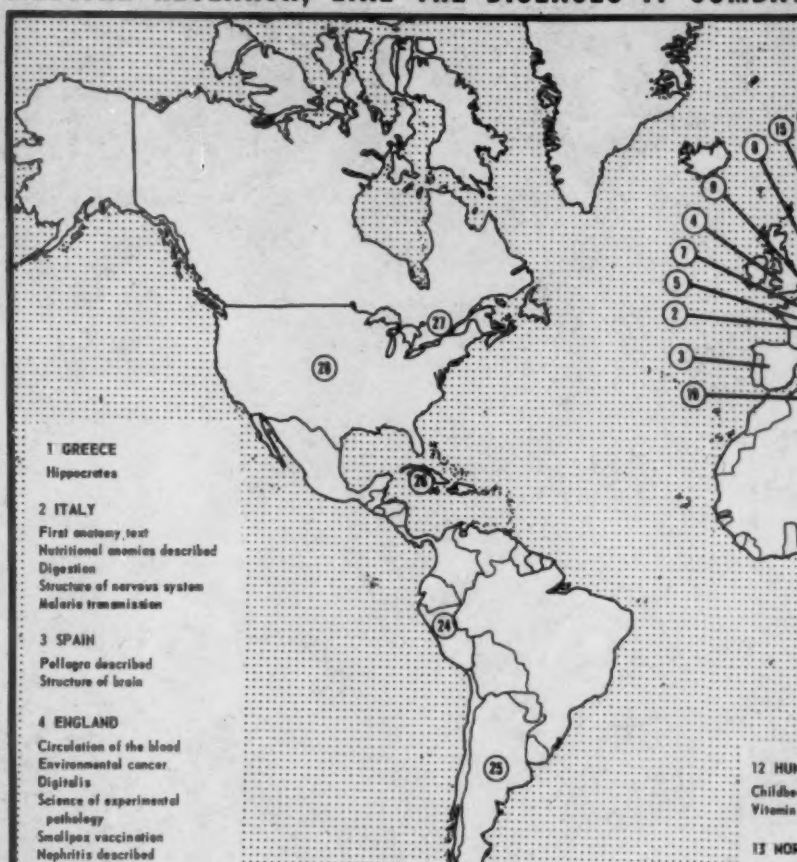
The drug, instrument or technique is tested on animals Treated animals are compared with nontreated "controls." Biochemistry, pharmacology, physiology, pathology and surgery serve this phase.

Third Stage
HUMAN

The finding is tried on patients in hospital or clinic. Physicians, biochemists, pathologists and others must work in a team. Tested products may be returned to the lab or made available for medical practice

SCIENCE IS INTERNATIONAL

MEDICAL RESEARCH, LIKE THE DISEASES IT COMBAT



1 GREECE
Hippocrates

2 ITALY
First anatomy text
Nutritional anemias described
Digestion
Structure of nervous system
Malaria transmission

3 SPAIN
Pellagra described
Structure of brain

4 ENGLAND
Circulation of the blood
Environmental cancer
Digitalis
Science of experimental pathology
Smallpox vaccination
Nephritis described
Cholera transmission
Theory of evolution
Antiseptic surgery
Chemistry of muscle
Vitamin research
Cancer-causing chemicals
Penicillin
World influenza Centre

5 FRANCE
Stethoscope
Science of neurology
Pasteurization
Vaccines for anthrax, rabies, tuberculosis
Role of hormones
Radium
First experimental cancer (X ray)
Chlorpromazine

6 GERMANY
Cell theory
Science of cellular pathology
Science of bacteriology
Tubercle bacillus
X ray
Chemistry of proteins, carbohydrates
Syphilis organism
Wassermann test for syphilis
Salvarsan
Diphtheria antitoxin
Cell respiration
Sulfa drug

7 SWITZERLAND
LSD for inducing psychosis
Salt-regulating hormone

8 HOLLAND
Microscope
Electrocardiograph
Vitamin research

9 BELGIUM
Pathology of nervous system

10 AUSTRIA
Science of genetics
Modern abdominal surgery
Psychoanalysis
Epidemic encephalitis described
Diuretics for heart failure

11 POLAND
Cell division

12 HU
Childbe
Vitamin

13 NO
Leprosy

14 SW
Salt ba
Lens o
Electro
Colloid
Heart s

15 DE
Staining

16 RU
Condit
First t
Theory
Discov
Experi

32489 O - 58 (Face p. 116)

NOTE.—This chart is intended for purposes of highlighting a few key act
tively the innumerable contributions made by nationals of the respective cou

COMBATS, KNOWS NO GEOGRAPHIC BOUNDARIES

12 HUNGARY
Childbed fever transmission
Vitamin C

13 NORWAY
Leprosy organism

14 SWEDEN
Salt balance discovered
Lens of the eye explained
Electrophoresis
Colloid chemistry
Heart surgery

15 DENMARK
Staining of bacteria

16 RUSSIA
Conditioned reflex
First tumor transplant
Theory of immunity
Discovery of viruses
Experimental arteriosclerosis

17 PERSIA
First medical text

18 INDIA
Cholera vaccine
Reserpine

19 MALTA
Undulant fever

20 AFRICA
Sleeping sickness transmission
Diet and heart disease

21 CHINA
Opium

22 JAPAN
Dysentery organism
Leptospira (Weil's disease organism)
Experimental chemical cancer

23 AUSTRALIA
Q fever described
Virus research
Congenital defects from German measles during pregnancy

24 PERU
Trephining
Quinine
Coca leaves as analgesic

25 ARGENTINA
Chemistry of diabetes

26 CUBA
Yellow fever transmission

27 CANADA
Insulin
Stress theory of disease
Brain surgery

28 UNITED STATES
Ether as anesthetic
Yellow fever control
Blood groups discovered
Allergy described
Iodine for goiter
Tissue culture
Experimental virus cancer
Tests and vaccines for infectious diseases
Cancer genetics
Hormone research
Rickettsial disease research
Cause and cure of pellagra
Brain surgery
Liver for pernicious anemia
Vitamin research
Fluoridation
Heart surgery
Streptomycin
First anticoagulant
Antimalarial drugs
Tracer studies of metabolism
Cancer chemotherapy
Steroids for arthritis
Study of molecular diseases
Polio vaccine

ew key activities only. It does not, of course, presume to convey either quantitatively or qualita-
ective countries in the field of international health.